

Preface

Product design has been widely recognized by the chemical engineering community to be a fertile area for further development. There is a sense of urgency because of a general feeling that the commodity chemicals sector, despite its economic significance and unabated innovations, has reached its maturity. The impetus is basically the need to create employment opportunities for our graduates, particularly those who decide to enter the workforce with a bachelor's degree. Similar to the growing presence of chemical engineers in the electronics and pharmaceutical industries, chemical engineering is expected to significantly increase its contribution to industrial sectors such as personal care products, foods, soaps and detergents, textiles and garments, home appliances, medical devices, among others.

As the focus shifts towards consumer products, three issues need to be considered. One is what to make. While it is obvious that the decision is driven by market demand, one has to have a firm grasp of the technical details and market trends of specific product types to be effective at work. Another is how to make. The engineer has to delve deeper into molecular design and material properties on the one hand and microstructures and macroscopic geometrical features on the other, in order to deliver a product with the desired attributes. The third issue is workflow. With relatively short product life cycle and considerable demand on interdisciplinary collaboration in product design and manufacturing processes, it is highly desirable to clarify the role of the chemical engineer, and that of the collaborators, in the various product value chains.

Chemical engineering has traditionally focused on commodity chemicals in its research and education. Most of its teaching materials are related to the design of chemical plants and petroleum refineries. Although much has been achieved by Cussler and Moggridge, and Seider, Seader and Lewin in their books to fill this void, more needs to be done to cover the numerous product areas. Most importantly, we have to clearly identify, and to develop if necessary, all the principles, skills and tools that the chemical engineers should know in order to perform on their job in various product sectors.

The objective of this book is to help form a more clear perspective of product design through case studies from people with different backgrounds. Products ranging from molecules to structured products are considered. Also, some cases studies involve products that have been commercialized, while some are student

projects illustrating how they work through a product design problem. Thus, researchers and engineers might benefit from the articles with in-depth treatment of a particular product. Educators and students can use the case studies in this book as a starting point for further investigations.

The articles of this book have been grouped into 3 parts. Part I focuses on the relationships between molecular structure and properties. Tailoring molecular structure for an intended application is a principal component in product design. Part II describes the design and manufacture of various structured / multicomponent products. A key feature for consumer products is the assessment of qualitative product qualities that are required to satisfy the consumers' wants and needs. Part III contains student design projects as well as views for the further development of product design.

We would like to thank all the contributing authors for their manuscripts. They represent a wide variety of views and expertise. The support of Elsevier in publishing this book should also be acknowledged. Finally, we hope that this book will contribute in a small way to the evolution of product design in chemical engineering practice and education.

Ka M. Ng, Rafiqul Gani and Kim Dam-Johansen

List of Contributors

Author	Address
Luke E.K.Achenie	Department of Chemical Engineering, University of Connecticut, Storrs, CT-06269 USA achenie@engr.uconn.edu
Keith K.H. Choy	Department of Chemical Engineering the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, P.R. China kechoy@ust.hk
Kurt A. Christensen	Haldor Topsøe A/S, Nymøllevej 55, Lyngby, DK-2800, Denmark kc@topsøe.dk
Luis A. Cisternas	Chemical Engineering Department, University of Antofagasta, Casilla 170, Antofagasta, Chile lcisternas@uantof.cl
Leonidas Constantino	Frederick Research Center, P.O. Box 24729, Nicosia, Cyprus ConstantinouL@cprl.com.cy
Peter Crafts	AstraZeneca Pharmaceuticals Ltd., Process R&D, Macclesfield, Cheshire, SK10 2NA, United Kingdom Peter.Crafts@astrazeneca.com
Kim Dam-Johansen	Department of Chemical Engineering, Technical University of Denmark, Building 229, DK-2800 Kgs. Lyngby, Denmark kdj@kt.dtu.dk
Rafiqul Gani	Department of Chemical Engineering, Technical University of Denmark, Building 229, DK-2800 Kgs. Lyngby, Denmark rag@kt.dtu.dk
Michael I. Hill	M. Hill & Associates LLC, Mahwah, NJ, USA michael@mhillassoc.com
Arunprakash T. Karunanithi	Department of Chemical Engineering, University of Connecticut, Storrs, CT-06269 USA
Søren Kiil	Department of Chemical Engineering, Technical University of Denmark, Building 229, DK-2800 Kgs. Lyngby, Denmark sk@kt.dtu.dk
F. Michiel Meeuse	Unilever Food and Health Research Institute, Olivier van Noortlaan 120, 3133 AT Vlaardingen, The Netherlands Michiel.Meeuse@Unilever.com

Ka Ming Ng	Department of Chemical Engineering the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, P.R. China kekmng@ust.hk
Lone Kierstein Nielsen	Novozymes a.s., Liquid Products Development, DK-2800 Bagsværd, Denmark
Albert J. Post	Unilever Research and Development, Trumbull, CT, USA
Warren D. Seider	Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104-6393, USA seider@seas.upenn.edu
Ole Simonsen	Novozymes a.s., Solid Products Development, DK-2800 Bagsværd, Denmark OSi@novozymes.com
Talid Sinno	Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104-6393, United States
Vassilis Vassiliades	Department of Chemical Engineering, Cambridge University, UK
Claus E. Weinell	Hempel A/S, Lundtoftevej 150, DK-2800 Kgs. Lyngby, Denmark
Diego M. Yebra	Hempel A/S, Lundtoftevej 150, DK-2800 Kgs. Lyngby, Denmark
King Lun Yeung	Department of Chemical Engineering, the Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong, P.R. China kekyeung@ust.hk

Chapter 1

Chemical Product Design – A Brief Overview

Rafiqul Gani^a, Kim Dam-Johansen^a & Ka M. Ng^b

^a*Department of Chemical Engineering
Technical University of Denmark
Building 229, DK-2800 Lyngby, Denmark*

^b*Department of Chemical Engineering
Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong, P.R. China*

1. 1 INTRODUCTION

In chemical product design and development, one first tries to find a candidate product that exhibits certain desirable or targeted behavior and then tries to find a process that can manufacture it with the specified qualities. The candidate may be a single chemical, a mixture, or a formulation of active ingredients and additives. For the later product type, additives are usually added to an identified active ingredient (molecule or mixture) to significantly enhance its desirable (target) properties. Examples of chemical products, such as functional chemicals (solvents, refrigerants, lubricants, etc.), agrochemicals (pesticides, insecticides, etc.), pharmaceuticals & drugs, cosmetics & personal care products, home and office products, etc., can be found everywhere. In this chapter and this book, the term “chemical product design” will be used to also include some aspects of “chemical product development”. Also, unless otherwise specified, the term “product” in this chapter will only include various types of chemical products.

Even though it is possible to identify many chemicals or their formulations as potential chemical products, only a small percentage actually become one. Finding a suitable process that can reliably, efficiently and economically manufacture the identified chemical with the desired product qualities as well as

evaluating product performance during application and analyzing market trends play important roles in product design and development. From a process point of view there are products where the reliability of the quality of the manufactured chemical may be the deciding factor (for example, drugs & agrochemicals), while there are others where the cost of manufacturing the product is at least as important as the reliability of the product quality (solvents, refrigerants, lubricants). This means that product-centered process design is important because identifying a feasible chemical product is not enough, it needs to be produced through a sustainable process. Also, while in the case of functional chemicals, the identified molecule or mixture is the final product, in the case of chemicals based consumer products (drugs, cosmetics & personal care products, etc.), they are intermediate products from which the final products are obtained through additional processing. Finally, the performance of the manufactured product, when applied, needs to be tested and validated. For some functional chemical products (such as solvents and refrigerants) this may be straight forward, but for some consumer products (such as drugs and food-products), it may not be so straight forward.

1.1.1 Chemical Product – Process Design

Chemical product design typically starts with a problem statement with respect to the desired product qualities, the needs and a set of target properties that define them. Based on this information, alternatives are generated, which are then tested and evaluated to identify the chemicals and/or their mixtures that satisfy the desired product specifications (qualities, needs and cost). This could be regarded as the *discovery* step. The next step is to select one of the product alternatives and design a process that can manufacture the product. This could be regarded as the product-process *development* step. The final step involves the analysis, test and validation of the product and its corresponding process. This could be regarded as the product *manufacturing & launch* step.

Chemical process design, as it is commonly known, typically starts with a general problem statement with respect to the chemical product that needs to be produced, its specifications that need to be matched, and the chemicals (raw materials) that may be used to produce it. Based on this information, a series of decisions and calculations are made at various stages of the design process to obtain first a conceptual process design, which is then further developed to obtain a final design, satisfying at the same time, a set of economic and process constraints. The important point to note here is that the identity of the chemical product and its desired qualities are known at the start but the process (flowsheet/operations) and its details are unknown.

Some of the important features of product-process design are the following:

- At the start, the identity of the chemical product is not known but the desired product specifications (targeted behavior) are known.
- Process design can be considered as an internal sub-problem of the total product design problem in the sense that once the identity of the chemical product has been established, the process and/or the sequence of operations that can produce it, needs to be determined.
- Product performance as well as issues related to supply chain, marketing, etc., need to be addressed. It may also be necessary to evaluate not only the product but also the process in terms of environmental impact, life cycle assessment and/or sustainability, before it can be launched.

1.1.2 Integration of Product-Process Design

From the above descriptions of product-process design, it is clear that some aspects of product and process design are linked. Also, product design is linked to product performance just as process design is linked to process performance (operation). Figure 1 illustrates these links by highlighting the interest in a process that is capable of manufacturing a product having the desired qualities and functions that match the targeted product performance.

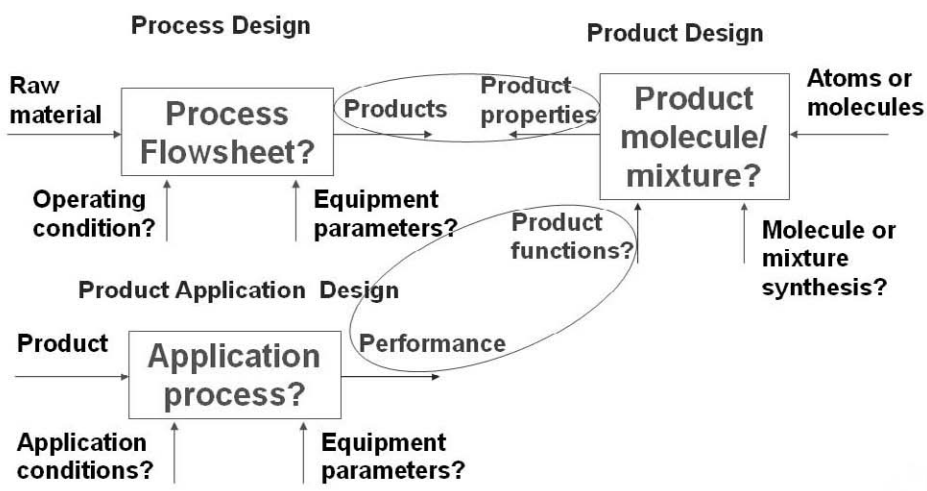


Figure 1: Links between product-process design and product-application design

Another interesting link between product-process design is the following - high value (low volume) chemical products require close monitoring of product quality for a fixed set of process (batch) operations, while low value (high volume) chemical products require close monitoring of product quality that is matched by changing the process (continuous) operations, when necessary. This means that for some chemical products (such as drugs and food-products), once the process details are fixed, they cannot be changed, making thereby, the achievement of first time right with respect to their manufacture, a primary target. For other chemical products (such as intermediate chemicals) the processing conditions can be manipulated in order to control the product quality. In the first case, on-line monitoring schemes keep the materials being processed and their corresponding processing steps at their specified (and approved) design to ensure that the product with the specified quality would be obtained. In the second case, on-line monitoring schemes take corrective actions by manipulating the processing conditions to ensure that the specified product will be obtained. In both cases, process economics and operability as well as issues related to sustainability and environment play important but different roles.

1.1.3 Stages of Chemical Product-Process Design

As pointed out by Gani (2004a), integration of the product and process design problems can be achieved by broadening the scope of a typical process design problem to include at the beginning, a sub-problem related to chemical product identification and to include at the end, sub-problems related to product and process evaluation, including, lifecycle and/or sustainability assessments. Gani (2004a) also proposed a modified version of Cussler and Moggridge's (2001) main stages of product design, which is highlighted through Fig. 2 [see also Wesseling, Kiil and Vigild (2005)]. Recently, Cordiner (2004) and Hill (2004) have highlighted various issues related to product-process design with respect to agrochemical products and structured products, respectively. Issues related to multi-scale and chemical supply chain have been highlighted by Ng (2001) and Grossmann (2004), respectively.

According to Fig. 2, during the "pre-design" stage, the needs and goals of a product are defined through a set of essential, desired and EH&S (environmental, health and safety) properties. In the "product-design" stage, the candidate molecules and/or mixtures that satisfy the desired (target) properties, are determined. In the "process-product design" stage, processes that can

manufacture the identified product are determined and from it, the optimal is selected. Issues related to the actual manufacturing of the product through the designed process and associated topics (on-line monitoring and control of product quality) are also addressed in this stage. In the “product application” stage, the performance of the product when applied, is evaluated. Note that since there are feedbacks between the product and process design stages, simultaneous as well as sequential approaches are applicable.

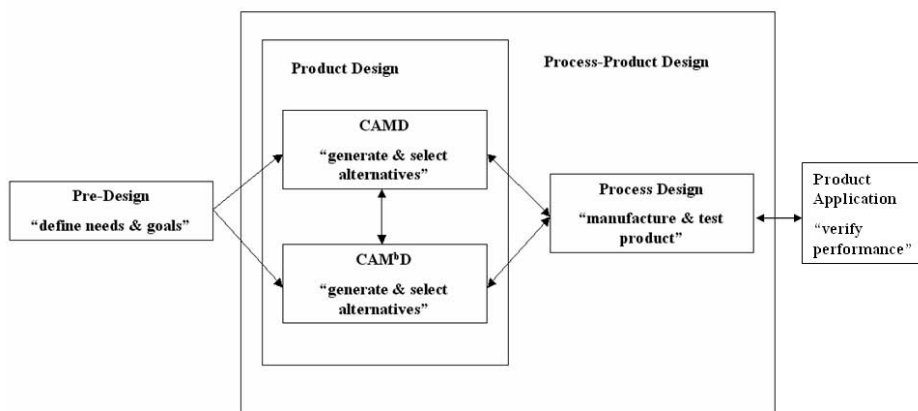


Figure 2: Different stages of product design and development

1.2 CHEMICAL PRODUCT DESIGN – SOLUTION APPROACHES

In principle, problems related to chemical product design can be formulated and solved in many different ways. The objective here is to highlight some of those that have also been applied in the various product design case studies reported in chapters 2-15 of this book. These solution approaches may be classified under the following types:

- Experiment-based trial and error – This approach is used when mathematical models for the estimation of the desired (target) properties are not available. A large number of consumer products are developed through experiment-based trial and error approaches. In this case, the desired properties need to be measured and consequently, not many candidate molecules can be considered. A list of candidate molecules may however be supplied by an expert or generated from past knowledge and/or experience. A database of chemicals may also be used to generate a list of candidates.

- Model-based search techniques – This approach is used when validated mathematical models for the estimation of all desired properties are available. In this case, a list of chemically feasible molecules and mixtures can be very efficiently and quickly generated and tested. Final selection depends, among others, on the corresponding process design, operational issues and product performance evaluation. Availability of models have contributed to the development of model-based computer aided molecular design (CAMD) and computer aided mixture/blend design (CAM^bD). These techniques are very suitable for design of functional chemicals where a large collection of property models can be found. More details on CAMD and CAM^bD can be found in Achenie et al. (2002) and Gani (2004b).
- Hybrid experiment-model based techniques – By far the largest number of chemical product design problems are solved through some form of a hybrid experiment-model based technique. These techniques are used when mathematical models are not available for all desired properties and/or product-process performance evaluations. One option then is to use the mathematical models to generate and test alternatives in order to identify a small number of candidates, which may be further investigated through the experiment-based trial and error approach. In this way, the search space is reduced and reducing thereby, the time and resources spent on the needed experimental effort.

1.2.1 Design of Molecule or Mixture for a Desired Chemical Product

These product design problems are typically formulated as,

Given the specifications of a desired product, determine the molecular structures of the chemicals that satisfy the desired product specifications, or, determine the mixtures that satisfy the desired product specifications.

The design/selection of functional chemicals (refrigerants and solvents) are common examples of these chemical product design problems. The design/selection of the active ingredients (AI) in the case of pharmaceutical, food and other consumer products is more complex as the size of the molecules are usually larger and the estimation and/or measurements of desired (target) properties more difficult. In the case of mixtures (blends and/or formulations), the chemicals comprising of AIs and additives may already be known and it is usually desired to find the identities of the chemicals that will be present in the final product (mixture) together with their compositions.

These two molecular-mixture design problems are also typically known as the reverse of property prediction, where, given the properties of the molecule or mixture, the objective is to identify the candidate molecules-mixtures that match them. Consequently, an iterative solution strategy where feasible alternatives (molecules and/or mixtures) are generated and tested to verify if their properties satisfy the target (properties are evaluated through reliable property estimation methods). The molecular design problem, as formulated above, is mainly employed to identify functional chemicals that are added to the process-product, such as solvents, refrigerants and lubricants and may be used by the process to manufacture a chemical product. In the case of mixture design, petroleum blends and solvent mixtures are two examples where the product may be designed with or without process constraints.

In the design of more complex chemicals, such as, the AI for consumer products, hybrid experiment-model based techniques are most appropriate as a combination of computations and experiments are needed to solve these problems. For example, in drug design, structures of “synthetic candidates” of a lead biologically active compound may be identified through molecular design. The generated synthetic candidates help to establish the activity of the “parent molecule” representing the lead chemistry. In this way, much time and resources are saved during the development of lead biologically active compounds. QSAR (Quantitative Structure-Property Relationships) techniques may be used to establish the relationships between the biological activity of the molecules, some characteristic properties of the molecules (such as the octanol-water partition coefficient) and the molecular structural parameters. The optimal AI can then be determined by generating similar molecular structures as the parent molecule and then locating the one having the minimum concentration in the protein. Note also that in all three types of solution approaches, databases may be used, if they are available.

1.2.2 Design and Development of Chemical Products

1.2.2.1 Structured products and formulations

Structured products, such as cosmetics, detergents, surfactant foams, inks, paints, drugs, foods and agrochemicals, combine several functions and properties in a single product. Design of these structured products involve the creation and the control of the particle size distribution in operations such as crystallization, precipitation, generation of aerosols, and nanoparticles as well as

control of the particle morphology and the final shaping and presentation in operations such as agglomeration, calcinations, compaction, and encapsulation [Charpentier (2003)]. In this case, the complex media (polymers, colloids, microemulsions, etc., where rheology and interfacial phenomena play an important role) and the particulate solids (ceramic pastes, foods, solid foams, gels, etc.) control the end-use property of the product as well as the product quality (defined in terms of taste, feel, smell, color, etc.). Consequently, these problems involve different scales of size, time and complexity. The key to success in the design of structured chemical products is to first identify the desired end-use properties of the product and then to control the product quality by controlling the microstructure formation. Solution of these problems require a hybrid multidisciplinary approach involving, for example, fundamental issues (interfacial phenomena, phase equilibria, kinetics, etc.), product design issues (nucleation growth, stabilization, additive, etc.), process design issues (design of operation, mass-energy balance, equipment sizing, etc.) and process control issues (sensors, quality monitoring, etc.).

An interesting example of a food product reported by Schubert [as described by Charpentier (2003)], where the quality of a food product is controlled by controlling the growth of microorganisms that could spoil the product. This is achieved by enclosing the microorganisms in a water-in-oil emulsion of aqueous droplets of a specific size. As pointed out by Schubert, special processing techniques are needed to generate the microemulsions (see also chapters 6 and 9 for examples of different aspects of structured product-process design). A hybrid experiment-model based approach has been developed to solve this problem. Control of size and shape of crystals in an industrial crystallization process can also be cited as an example of structured product design.

1.2.2.2 Other chemical products

In these design problems, given, the specifications (qualities and needs) of a desired chemical product, the objective is to identify the chemicals and/or mixtures that satisfy the given product specifications, the raw materials that can be converted to the identified chemicals, and a process (flowsheet/operations) that can manufacture them sustainably, while satisfying the economic, environmental and operational constraints. Alternatively, processes and products would need to be matched from a list of candidate chemicals and processes in order to determine the optimal product-process combination. This design problem may also be termed as product-centric process design [Fung & Ng (2003); Harjo et al. (2004); Wibow & Ng (2001)]. See also Ulrich & Eppinger (2000) for a good overview on product design and development.

As illustrated in Figure 3, solution of these problems could be broken down into three sub-problems, a chemical product design problem that only identifies the chemicals (typically formulated as a molecule or mixture design problem), a process design part that determines a process that can manufacture the identified chemical or mixture (typically formulated as a process design problem) and a product-process evaluation part (typically formulated as product analysis and/or process analysis problems). In principle, mathematical programming problems can be formulated and solved to simultaneously identify the product and its corresponding optimal sustainable process. The solution of these problems are however not easy, even if the necessary models are available [Gani (2004a)]. The main difficulties, as pointed out by Cordiner (2004) for the agrochemical products sector, are caused by the lack of a systematic effort to measure and collect data for the development of models that could be used in model-based techniques for product-process development.

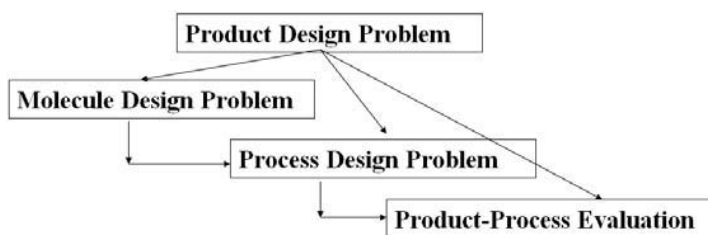


Figure 3: Decomposition of the product design problem.

Numerous examples of new alternatives for the production of known chemical products can be found in the open literature and have been successfully addressed by employing a model-based technique. Examples of complete product-process design for new high-value chemical product, however, is not easy to find because of reasons of confidentiality. Still, interesting examples of some well known high value bio- and chemical products from the pharmaceutical and specialty chemical industries can be found, for example, design and manufacturing of penicillin [Queener and Swartz (1979)]; production of intracellular protein from recombinant yeast [Kalk and Langlykke (1985) and Blanch & Clark (2007)].

1.2.3 Evaluation in Chemical Product Design

In these problems, given a list of feasible candidates, the objective is to identify/select the most appropriate product based on a set of product performance criteria.

This problem is similar to CAMD or CAM^bD except for the step for generation of feasible alternatives. Also, usually the product specifications (quality and needs) can be sub-divided into those that can be used in the generation of feasible alternatives and those that can be used in the evaluation of performance. A typical example is the design of formulated products (also known as formulations) where a solvent (or a solvent mixture) is added to a chemical product to enhance its performance. Here, the feasible alternatives are generated using solvent properties while the final selection is made through the evaluation of the product performance during its application. Consider the following problem formulations:

- Select the optimal solvent mixture and the paint to which it must be added by evaluating the evaporation rate of the solvent when a paint product is applied [Klein et al. (1992)].
- Select the pesticide and the surfactants that may be added by evaluating the uptake of the pesticide when solution droplets are sprayed on a plant leaf [Munir (2005)].
- Select the active ingredient (AI) or drug/pesticide product and the microcapsule encapsulating it by evaluating the controlled release of the AI [Muro-Sune et al. (2005)] through the microcapsule.
- Select solvent mixtures for crystallization of drug or active ingredient [Karunanithi et al. (2006)]. See also chapters 2 and 4.

In all the above design problems, the manufacturing process is not included but instead, the application process is included and evaluated to identify the optimal product. Note that the formulated product, which may also be defined as products that are sold based on their properties during use and not their molecular structure, may need to pass a set of quality tests.

Consider the following product design and evaluation problem from the agrochemical industry. A pesticide product consisting of an active ingredient and an additive need to be evaluated in terms of its controlled release characteristics from a polymeric microcapsule to a release medium. Here, since the AI and the additives (solvent and surfactant) are known, the product-evaluation problem consists of designing the microcapsule and identification of

the polymer (molecular/mixture design), determining the loading of the microcapsule with the AI (process measurement and/or process design - modeling), and, the controlled release of the AI from the microcapsule (product performance evaluation). Figure 4 illustrates the three sub-problems that need to be solved. For each sub-problem, experiments would need to be performed if the appropriate property-process models were not available. A systematic effort is necessary to collect data; to develop models for prediction of pure polymer (repeat unit) properties, polymer solutions and controlled release performance based on the collected data and a good understanding of the product-process-performance characteristics; and, finally to use the developed models for screening of alternative pesticide formulations and microcapsules so that the pesticide product and the optimal microcapsule design can be identified simultaneously. Muro-Sune et al. (2005) provides details of model-based computer-aided design for controlled release of pesticides. Using a similar approach, the uptake of a pesticide AI from a water droplet into a plant leaf can be investigated as a function of the additives needed to enhance the uptake rate. In both cases, an integration of methods, models and tools is necessary to identify the optimal design.

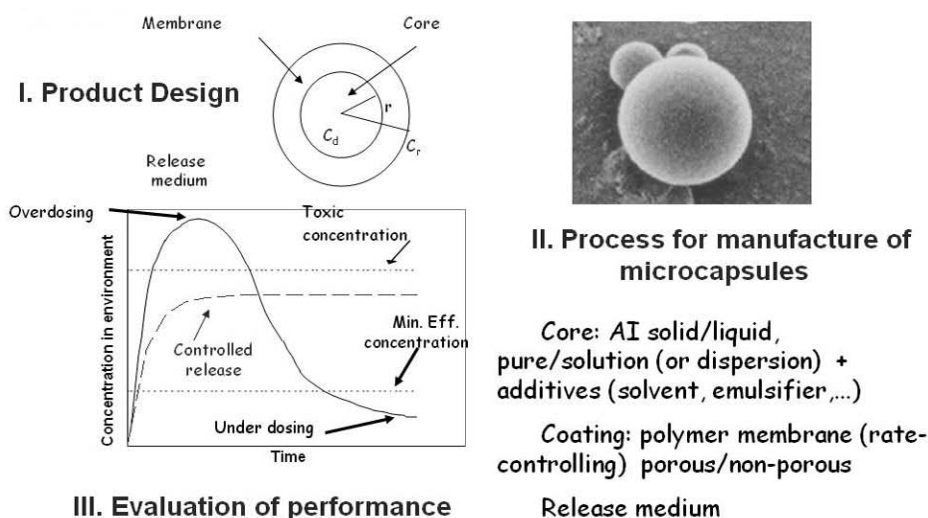


Figure 4: Illustration of simultaneous product design (polymeric membrane), process evaluation and product performance in terms of controlled release of a pesticide product.

1.3 IMPORTANT ISSUES & NEEDS IN CHEMICAL PRODUCT DESIGN

Some of the important issues and needs for chemical product design are discussed in this section with respect to the main stages of the product design problem highlighted in Figure 2. That is,

- How to define the goals and needs of a chemical product in terms of a set of desired (target) properties?
- How to identify a set of product candidates that will define the search space where the optimal product may be found?
- How to determine the process that can manufacture the desired product with the specified quality and optimal cost?
- How to evaluate the process and product performance?

1.3.1 *Definition of Product Goals*

A systematic method to identify the properties through which the goals and needs of chemical products is currently not available. Databases and CAMD techniques applied to the design of functional chemical products (refrigerants, solvents for extraction, solvents in organic synthesis, solvents for cleaning, solvents in formulations and polymers with specific end-use properties) have been reported [see Achenie et al. (2003)]. Much work is needed, however, to extend these methods to cover a wide range chemical products. A good understanding of the issues, such as the relation of end-use properties defining the performance of a chemical (product) to its microscopic and macroscopic structural parameters and the phenomena governing the product-process characteristics. For example, which end-use properties of a structured product can be controlled, does solvents have any influence on the shape of crystals to be formed, which properties of polymeric membranes in microcapsules define its performance during controlled release of the AI and many more. An important first step is to collect information from known (or published) case studies and store them in a suitable database with an appropriate search engine for data retrieval.

1.3.2 *Identification of Product Candidates*

In this case, systematic methods for generation of feasible molecular and mixture candidates have been reported for the design of functional chemical products [see Achenie et al. (2003)]. Methods based on database search, total enumeration of feasible candidates (rule-based techniques that avoid a combinatorial explosion), mathematical programming, genetic algorithm, and,

statistical optimization, have been reported and successfully applied for design of solvents, refrigerants, process fluids and polymer repeat units. For larger and more complex products, however, the number of combinations even after application of special rules, is too large (for example, the number of possible isomers for a C₉ primary alcohol alone is more than a million). Also, even if all the structures can be generated, to evaluate their target properties, property estimation methods that can distinguish between isomers and/or predict reliable property values for large, complex multifunctional molecules, would be necessary. Sufficient data needs to be collected to enable a systematic study of the properties that define the goals and needs of a product and for the development of appropriate mathematical models. Where experiments cannot be performed to measure the needed data, validated molecular modeling techniques could be used to generate pseudo-experimental data, specially the end-use properties as a function of the microstructure of the chemical product. Knowledge-based systems that can *a priori* screen-out redundant combinations, and therefore, reduce the combinatorial size of the search space would also make a big impact in terms of finding the optimal structured chemical product. Kontogeorgis and Gani (2004) provide a useful overview of model-based property estimation for chemical product design, including the need for data to model development and validation. Identification of AIs based on their desired activity as in drugs, food-products, cosmetics, etc., require hybrid experiment-model based techniques [see Reynolds et al. (1995)].

1.3.3 Identification of the Process Alternatives

This topic is discussed in detail in chapter 16 and therefore not discussed further in this section.

1.3.4 Product-Process Evaluation

As highlighted through Fig. 1, in addition to evaluation of the performance of the process, the performance of the product when it is applied, also needs to be evaluated. Depending on the type of the product-process, these can be model-based, experiment-based or a combination of both. The performance of functional products and the processes that manufacture them, are generally easier to evaluate than the consumer chemical products. The reason being that a greater amount of knowledge and available data have been converted to mathematical models that can be used for model-based performance evaluations. In the case of consumer chemical products, however, the available knowledge and data have not yet been converted into models that are suitable for model-based techniques. Also, because of the nature of the final consumer product and their manufacturing process, on-line monitoring and data analysis is

more appropriate for their performance evaluation. PAT (process analytical technology) systems, which are based on on-line analysis and monitoring of the product and process, are finding increasing use in the pharmaceutical, food and agrochemical industries. Finally, product evaluation based on the activity of the active ingredient, such as the activity of a drug or the taste of a food-product, is based on experiments involving human volunteers.

1.3.5 Framework for Product-Process Design

Even though we do not have sufficient knowledge to understand all aspects of product-process design, do not have sufficient data to resolve all product-process design issues and/or do not have versatile models or a sufficient large collection of models to cover a wide range of chemical products, it is still possible to solve many product-process design problems correctly, consistently and efficiently. What is important is to learn from past experience so that the next time, solution of similar problems will require a smaller effort. This can be achieved through a framework for product-process design that allows the use of the available knowledge, data, model, etc., in the most flexible and efficient manner. A simple version of this framework is illustrated in Fig. 5, where the main steps of product design and development are indicated in terms of the associated work-flow, the data-flow and the associated techniques, methods and tools. The parts where models may be developed and used, are also highlighted.

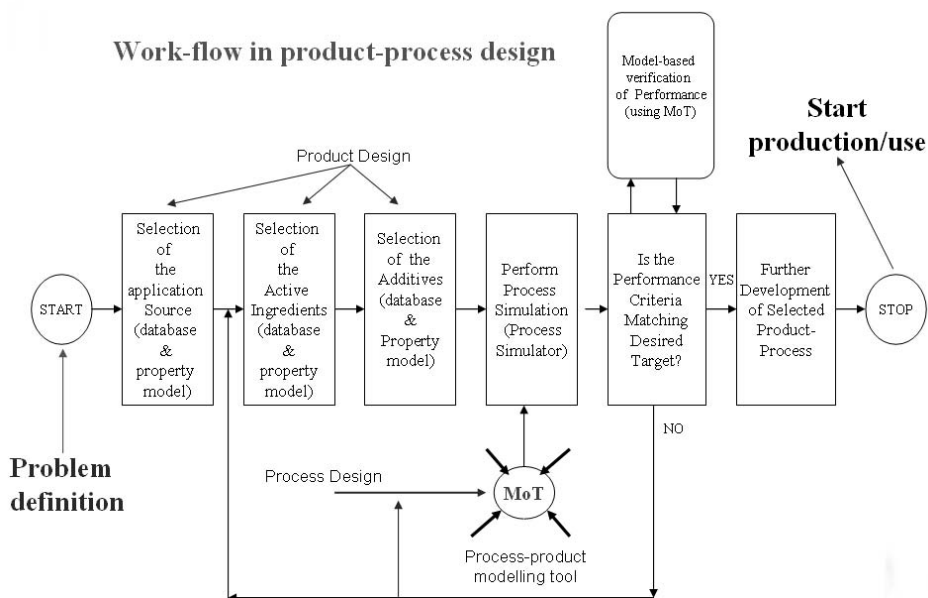


Figure 5: Framework for systematic product-process design and development

We start with a definition of the problem and based on this, we identify the candidates (such as, molecules, mixtures and formulations) through expert knowledge, database search, model-based search, or a combination of all. The next step is to perform experiments and/or model-based simulations (of product behavior) to identify a feasible set of candidates. At this stage, issues related to process design are introduced and a process-product match is obtained. The final test is related to product quality and performance verification. Other features, such as life cycle assessment could also be introduced at this stage.

1.4 CASE STUDIES

1.4.1 *Molecular and/or Mixture Design*

In this book, case studies highlighted in chapters 2, 3 and 5 involve chemical product design problems where relationships between molecular structures or mixtures and end-use (target) properties are investigated to identify the chemical product. In chapter 2, the role of solubility modeling and its application within the design framework of a pharmaceutical product (Cimetidine) is highlighted for an API crystallization step. A hybrid experiment-model based technique has been applied. In chapter 3, a computer aided molecular design technique has been employed to identify solvent replacements for the process industry. Experiments have been performed to validate the final selection. In chapter 4, a decomposition based computer aided molecular and mixture design technique has been employed to identify mixtures of solvents and anti-solvents for the multi-step crystallization of a pharmaceutical product (Ibuprofen). Again, experiments have been performed to validate the design. In chapter 5, a hybrid experiment-model based technique is employed to design a liquid detergent enzyme product with a built-in stabilization system that could be employed by a liquid detergent designer to avoid the addition of boric acid and thereby reduce the amount of polyols.

1.4.2 *Structured Product-Formulation Design*

The case study highlighted in chapter 9 involves the design and identification of a structured chemical product. In particular, the case study involves the design of a cleansing bar that did not leave a bathtub ring as well as recognition as a high quality personal cleansing bar characterized by properties such as firmness, rich creamy lather, absence of grit, not harmful to skin, without unpleasant odor

or color and low mush rate. The final consumer product, Dove®, is a well known product from Unilever.

1.4.3 Structured Product-Formulation Design

The case study in chapter 6 deals with the synthesis of processing steps needed in the manufacture of a multi-phase and structured food product. The challenge is to design a process that can produce the product having a specified arrangement of phases within a microstructure. Examples involving the manufacture of mayonnaise (which is an emulsion of about 80% oil in water, stabilized by egg yolk protein) and ice cream (a product that consists of four phases) are presented. The case study in chapter 8 proposes a product-centered approach which applies chemistry and chemical engineering principles to develop the manufacturing process of detergent products with the desirable performance. The products can have different delivery forms such as powder, tablet, spray, gel, unstructured liquid, and structured liquid. A systematic procedure is presented to provide guidelines for easier and faster product and process development, focusing on how to manipulate the detergent chemicals and the processes involved in response to consumer needs. The procedure highlights specific aspects unique to detergents, which were absent in the previously developed procedures for specialty chemicals in general. The case study in chapter 10 involves the manufacture of an industrial chemical product, epitaxial silicon wafers, used in the production of *configured consumer products* such as integrated circuits. This case study also discusses the process technology innovation issues such as the design of the plasma-enhanced, chemical-vapor-deposition (PECVD) reactor. The case study in chapter 11 discusses the steps involved in the design and development of a new SO₂ oxidation catalyst, which was introduced to the market in 1996 by Haldor Topsøe from Denmark.

1.4.4 Product Identification and Evaluation

The case study from chapter 7 is concerned with the design and improvement of chemically-active ship bottom paints known as antifouling paints. A hybrid experiment-model based approach is employed here. Experiments and use of expert knowledge are employed to identify product alternatives, whose evaluation in terms of performance as a marine biofouling protector is verified through a model-based approach.

1.4.5 Chemical Product Design Educational Modules

Several case studies that have been generated from teaching courses on chemical product design and may be used as educational modules in courses on chemical product design are given in chapters 13 and 14. In chapter 14, the case studies involve the use of computer aided methods and tools for chemical product design. In addition, chapter 12 describes the experience in teaching Chemical Engineering students in Hong Kong the basic elements of successful entrepreneurship and product design through the final year design project.

The chemical product used in the design project (chapter 12) is a household appliance designed to deliver clean air by removing and killing airborne microorganisms, and converting carbon monoxide and common VOCs found indoor into harmless carbon dioxide and water. It also dehumidifies indoor air and maintains a comfortable humidity level that suppresses fungal proliferation. The appliance is intended to maintain its performance without maintenance for at least two years and is expected to have a functional life of at least five years. The product contains an active formulation of (1) low temperature oxidation catalyst, (2) VOCs adsorbent and (c) desiccant.

Six chemical product design problems are presented together with the solutions developed by students from the University of Minnesota. These problems cover the following topics

- Optical currency substrate for counterfeit prevention
- Oxygen impermeable food wrap
- Controlled drug release
- Solid formulation of low melting point of active ingredients
- UV shield film
- Adhesives for wet metal surfaces

The use of computer aided methods and tools in chemical product design is highlighted in chapter 14 through several design/selection problems involving solvent design/selection, refrigerant design, polymer repeat unit design, mixture design and “backbone” design and evaluation. In all cases, the problem definition, the input specifications for the software used and the results are given. The software used is ICAS (Integrated Computer Aided System), which contains a number of toolboxes that are specially suited for some aspects of chemical product design.

Finally, chapter 15 proposes the development of a classification system for the available knowledge on chemical products that can serve as a guide in chemical product design, development and teaching. The chapter examines the nature of

chemical products and discusses some of the important issues related to chemical product design and development.

1.5 CONCLUSIONS

As chemical product design covers a wide range of products-processes and topics, it is not possible to cover all aspects within a single book or chapter. This chapter has tried to provide the reader with a brief overview of some of the important features of chemical product design. First, an introduction to chemical product design, its link to process design and the stages of product design have been discussed. This is followed by a classification of different types of problems related to chemical product design and a discussion on the issues and needs with respect to solution of various types of chemical product design problems. A framework for systematic computer aided chemical product design has also been proposed within the context of systematic chemical product design. Finally, the product design problems presented as case studies in chapters 2-14 of this book are briefly previewed, highlighting some of the issues discussed in this chapter.

Important messages to take from this chapter are the following:

- Product-process design are linked and in specific cases, there is an advantage to look at integrated solution approaches rather than sequential approaches.
- The solution approaches that are currently being applied to product-process design can be classified in terms of those that are experiment-based, model-based and combination of both (hybrid).
- While model-based techniques may be efficient, because of the lack of reliable models, knowledge and data, experiment-based is the one more commonly applied.
- A more practical approach is the hybrid approach where a combination of models (where applicable) and experiments (where models are not applicable) are employed. For hybrid approaches, development of a systematic method of solution based on a decomposition of the overall design problem into a hierarchy of tasks and sub-tasks is necessary.
- It is important to collect information on various chemical product design applications in the form of case studies, as they can help to understand the issues and needs related to the development of more efficient and versatile methods and tools. Also, they serve as examples in teaching of chemical product design.

REFERENCES

- Achenie, L. E. K., Gani, R., Venkatasubramanian, K. *Computer Aided Molecular Design: Theory and Practice*, CACE-12, Elsevier Science B. V., The Netherlands (2002).
- Blanch, H. W., Clark, D. S., Biochemical Engineering, 2nd Edition, Marcel Dekker, Inc., New York, USA (2006).
- Charpentier, J. –C. (2003) The future of chemical engineering in the global market context: Market demands versus technology offers, *Kem Ind*, **52** (9) 397-419.
- Cordiner, J. L. (2004) Challenges for the PSE community in formulations, *Computers and Chemical Engineering*, **29**, 83-92.
- Cussler, E. L. & Moggridge, J. D. *Chemical Product Design* Cambridge University Press (2001).
- Gani, R. (2004) Chemical product design: Challenges and opportunities, *Computers and Chemical Engineering*, **28**(12), 2441-2457.
- Gani, R. (2004) Computer aided methods and tools for chemical product design, *Chemical Engineering Research and Design*, **82** (A11), 1494-1504.
- K. Y. Fung, K. M. Ng, 2003, Product centered processing: Pharmaceutical tablets and capsules, *AIChE J.*, 49(5), 1193.
- Grossmann, I. E. (2004) Challenges in the new millennium: Product discovery and design, enterprise and supply chain optimization, global life cycle assessment, *Computers and Chemical Engineering*, **29**, 29-39.
- Harjo, B., Wibowo, C. & Ng, K. M. (2004) Development of natural product manufacturing processes: Phytochemicals, *Chemical Engineering Research and Design*, **82**(A8), 1010-1028.
- Hill, M. (2004) Product and process design for structured products: Perspectives, *AIChE J.*, **50**, 1656-1661.
- Kalk, J. Langlykke, A. (1986) Cost estimation for biotechnology projects, ASM Manual of Industrial Microbiology and Biotechnology.
- Karunanithi, A., Achenie, L. E. K. & Gani, R. (2006), A computer aided molecular design framework for crystallization solvent design, *Chemical Engineering Science*, **61**, 1243-1256.
- Klein, J. A., Wu, D. T. & Gani, R. (1992) Computer aided mixture design with specified property constraints, *Computers and Chemical Engineering*, **16**, S229.
- Kontogeorgis, G. & Gani, R., *Computer Aided Property Estimation for Process and Product Design*, CACE-19, Elsevier Science B. V., The Netherlands (2004).
- Munir, A. 2005, Pesticide product and formulation design, MSc-thesis, CAPEC, Department of Chemical Engineering, DTU, Lyngby, Denmark.
- Muro-Sune, N., Gani, R., Bell, G., Shirley, I., (2005b). Model-based computer-aided design for controlled release of pesticides, *Computers and Chemical Engineering*, **30**, 28-41.
- Ng, K. M. (2004) MOPSD: a framework linking business decision-making to product and process design, *Computers and Chemical Engineering*, **29**, 51.
- Queener, S. & Swartz, R. (1979) Penicillins; biosynthetic and semisynthetic, *Economic Microbiology*, **3**, Academic Press, 35-123.

- Reynolds, C. H., Holloway, M. K. & Cox, H. K. Computer-Aided Molecular Design – Applications in Agrochemicals, Materials and Pharmaceuticals, ACS Symposium Series, 589, Washington, DC, USA. (1995).
- Ulrich, K. T., and S. D. Eppinger, “Product Design and Development,” second edition, Irwin McGraw-Hill, Boston (2000).
- Wesselingh, J. A., Kiil, S. Z., Vigild, M. E., Innovate – Design (Bio-) Chemical Food and Pharma Products, Department of Chemical Engineering, Technical University of Denmark, 2005.
- Wibowo, C., Ng, K. M. (2001) Product oriented process synthesis and development: Creams and pastes, *AIChE J.*, **47**(2), 2746.
- Wintermantel, K. (1999 Process and Product Engineering: Achievements, Present and Future Challenges, *Chemical Engineering Research & Design*, **77**, 175.

Chapter 2

The Role of Solubility Modeling and Crystallization in the Design of Active Pharmaceutical Ingredients

Peter Crafts

AstraZeneca Pharmaceuticals Ltd., Process R&D, Macclesfield, Cheshire, SK10 2NA, United Kingdom

2.1 Introduction

This chapter provides an introduction to the pharmaceutical sector, and the business of developing new active pharmaceutical ingredients (API). Crystallization is the preferred method of isolating commercial API products because it offers a highly efficient means of purification. The crystallization process is also where the physical properties of the drug substance are defined. These properties can have a significant impact on the formulated product and process, and eventually on the drug release profile in the patient.

The science of crystallization and polymorphism is introduced at a level that assumes little prior knowledge of the subject. The key aspects are developed, and combined with recent advances in solubility modeling and prediction techniques, in the development of a generic design methodology for an API crystallization step. The role of solubility modeling and its application within the design framework is demonstrated with a case study on Cimetidine, using the non-random two-liquid segment activity coefficient model (NRTL-SAC) [1] and a group contribution based approach [2]. The design methodology will be relevant to other industries where the crystallization of large, functionally complex molecules is performed, as in the Fine, Specialty and Agrochemical sectors. The chapter concludes with a discussion of some unresolved challenges in the efficient design and modeling of crystallization processes.

2.1.1 *An Introduction to the Pharmaceutical Industry*

The non-generic pharmaceutical companies are focused on discovering, producing and marketing *new* drug products. Most of these products will have worldwide sales of between \$0.5 and \$5 billion US dollars per year, during their patent protected life. This high apparent profitability is balanced by an equally high risk of products failing during the clinical trials programme. On average only 21.5% of new drugs that enter clinical trials will ever make it to the marketplace, and the average cost of developing a new drug is currently estimated in the region of \$800 million when capitalized.

The critical path between nomination of a new drug substance and its entry to the marketplace is almost exclusively defined by the clinical trials programme. Typically this includes the following three phases:

- Phase I – Involves 20 to 80 patients and investigates drug toxicity in healthy volunteers. Outcomes are the maximum tolerated dose and API concentration profile in the body.
- Phase II – Involves 100 to 300 patients and confirms the proof of principal, using biochemical markers, followed by the proof of concept using effects on the disease or an induced form of the disease.
- Phase III – Involves 1000 to 3000 patients and confirms efficacy across a wide range of the population.

The clinical trials programme for a new drug is in direct conflict with its patent lifespan, which extends for twenty two years from the time that its clinical effect is first discovered. The average development time, from patent application to market entry, is seven to twelve years, leaving just ten to fifteen years of high value sales, and good profitability. This period is essential for the long term viability of a non-generic pharmaceutical company, because it funds the new product pipeline. Once patent expiry has occurred then the market is open for generic manufacturers to enter; with a secure and established marketplace they avoid the high risks and costs associated with the discovery process, enabling them to sell products at significantly lower margins.

One only has to glance at the daily papers to understand that the global pharmaceutical market is becoming tougher. Concerns about pricing and the risk to benefit profile of new drugs is reducing levels of profitability and driving efficiency improvements throughout the industry. In the Process R&D environment this translates to the need for new methods to help rapidly and effectively design new processes that are fit for purpose, easy to scale-up, with high quality and low inherent variability.

The cost of API drug substance (in raw material terms) in the early stages of development is typically in the range of \$3 to \$7 thousand per kg. This material is essential and in high demand for toxicological testing, formulation development and clinical trials. As a result of these factors, process research and development groups must employ novel techniques in the design and scale-up of new manufacturing processes. The application of predictive models and in-silico chemical engineering can play an important role in this process, however, more often than not the chemical complexity of the systems and minimal existing physical properties data limits their application. The appearance of new thermodynamic models like NRTL-SAC [1] and the evolution of group contribution based methods, through tools like ProCAMD and SoluCalc [3, 4], now offers the potential for significant improvements to be made in process design efficiency.

The design of a process to consistently deliver product of high quality, that meets the rigorous standards of the regulatory authorities is of paramount importance to the industry. Once in production the cost in raw material terms for a single batch of API is typically \$1 to \$2 million, and failure of a batch to meet specification will incur significant cost. This loss is compounded in the early launch phase of a new product, if manufacturing issues lead to an inability to supply the market. The importance of robust crystallization on the supply chain is highlighted in the Ritonavir example that follows in section 3.6.2. This case highlights both the impact and considerable difficulties involved in identifying and controlling the polymorphic form of an API. Polymorphism is a field of research where there is a requirement to develop further understanding at the molecular level and develop robust design methodologies.

The following sections of the introduction identify the design constraints that are of particular importance to the pharmaceutical industry.

2.1.1.1 Quality

Product quality, purity and consistency are critically important in the pharmaceutical sector, applying to all stages of the supply chain and final dosed product. The human body is an exceptionally complex system and the full effect of a pharmaceutical product, consisting of the API, impurities and formulation components, is impossible to predict from first principles. The industry relies on rigorous clinical trials to assess drug efficacy, toxicity and side effect profiles.

When designing a new manufacturing process it is essential to understand the entry point and fate of all potential impurities on the process; these include impurities in the registered starting materials, those generated by side reactions, and many causes that would be insignificant in most related industries;

leaching from plastics and elastomers seals; low level bacterial and fungal contamination from process water or water damp solids; trace metals from corrosion products etc. All of these aspects are rigorously controlled through the application of “current Good Manufacturing Practice” (cGMP) standards. These incorporate the necessary procedural controls and documentation, together with training and cultural aspects.

2.1.1.2 Regulations and Manufacturing Flexibility

The pharmaceutical industry is closely regulated by national groups such as the US Food and Drug Administration (FDA), to ensure the necessary quality standards are achieved. All relevant aspects of the development and manufacturing process must be rigorously documented and fully auditable. Once a New Drug Application has been submitted to the regulatory authorities for approval to launch, it becomes very costly to make even relatively minor changes to a manufacturing process, therefore it is important to get the process design *right first time*.

Quality and regulation are the most significant differentiators between the Pharmaceutical sector and the Specialty Chemical and Agrochemical sectors; all of which employ the same basic production equipment and batch manufacturing techniques.

2.1.1.3 Batch Manufacturing

Batch manufacturing technologies are used almost exclusively by the non-generic pharmaceutical manufacturers. Batch integrity and trace-ability are important throughout the supply chain, minimizing the impact of abnormal events to discrete quantities of product. Material recycles are generally avoided because they introduce additional problems of quality control, particularly in respect of impurity concentrations. To compensate for this, most synthetic chemistry is designed to be high yielding and highly selective. Solvent recycles are contracted to outside specialists to minimise the environmental load. Because of the small production volumes of many API it is typical for production campaigns to be run in multi-product plants that are furnished with generic equipment. Processes are designed to fit these generic arrangements where feasible.

2.1.1.4 The Importance of Crystallization

Crystallization is the obvious choice for purification, of both manufacturing intermediates, and the final API product. Most of these compounds have molecular weights in the range 200 to 600 g/mol, and normal melting

temperatures of 150°C to 350°C. Crystallization offers high purity, recovery and energy efficiency, whilst maintaining low environmental impact.

The final stage in most API manufacturing processes involves a single crystallization step that is usually referred to as the Pures stage. It achieves the desired level of chemical purity and removes plant debris that may have entered during the previous manufacturing steps. All equipment is built to the highest specifications and *all materials* that enters the final crystallizer and product isolation filter, including process nitrogen, are screened through micron rated cartridge filters. The production rooms which house this Pures equipment are designed to prevent contamination during product discharge, packaging and maintenance activities, with dust free surfaces and HEPA filtered and conditioned air.

This final “Pures” step is the last stage of manufacture for the API and may be considered as the *API Product* design step. It will be the focus of this chapter’s case study, using the generic drug molecule Cimetidine as an example.

2.1.1.5 Formulation

The formulation science used in the manufacture of pharmaceutical products is a complex discipline in its own right, and largely outside of the scope of this chapter; only a very brief overview will be presented here.

Many different formulation types are used to deliver API to the patient; solid tablets, liquids, capsules, creams, inhalers, injections etc. The formulation choice is based on knowledge of the drugs mode of action, the required dose level, its optimal release profile, maximum tolerated dose and ease of use by the patient. Most of these properties are determined through the clinical trials programme. The pharmacokinetic behavior of a drug is particularly important, and characterizes the rate of transport of the API (or active metabolite) to its site of action in the body, against the concurrent processes of metabolism and excretion. The first step in this process for an oral dose is absorption of the API into the body, through the gastrointestinal wall and into the blood stream. This step is characterized by a drugs bioavailability.

The physical properties of an API can significantly effect the physical and chemical stability of a formulation, its bioavailability and ultimately they can modify the pharmacokinetic profile of the drug. This issue will be discussed in more detail in section 3.4. For these reasons it is necessary to control the physical form of the API at the Pures crystallization step, and throughout the subsequent formulation steps, to ensure a consistent delivery profile to the patient. This control strategy must be documented in the New Drug Application

paperwork that is submitted to the regulatory bodies, prior to their approval to launch a new drug product.

2.2 Crystallization Science

The defining characteristic of a crystalline solid is long range order. The basic crystal motif [5,6] may be composed of a single molecule or an arrangement of molecules, as in the case of a solvate or hydrate. Whatever the motif form, it will be regularly and uniformly distributed through all axis of the crystal. This is the reason that crystallization can achieve such high levels of purification; the growth and assembly process excludes molecules that do not closely match the motif.

The phenomena of crystallization can be understood through the established principles of thermodynamic equilibria and kinetic rate processes. For the design of a robust and scaleable crystallization process it is *essential that both of these effects* are considered.

2.2.1 Thermodynamics and Crystallization

The change in state from liquid to solid as a material crystallizes, is driven by thermodynamics and the principle of free energy minimization, in turn this results from a trade between the total enthalpy and entropy of a system.

Free energy is defined as:

$$G = H - T.S \quad \text{.....Eq 1.}$$

Where G is the Gibbs free energy, H is the enthalpy, T is the absolute temperature and S is the entropy.

As molecules from the liquid phase join together to form a crystal lattice the system becomes more ordered and the global entropy falls, with a corresponding increase in free energy. This is compensated by an decrease in system enthalpy and reduction in free energy as bonds form between the constituent molecules of the crystal lattice. This reasoning explains why a solid phase may be thermodynamically stable, and the preferred state for a system, but it is not sufficient to guarantee that a solid phase will actually form. It is well documented that high purity water can be cooled significantly below 0°C without the formation of ice, and can be held in this metastable state indefinitely.

2.2.2 Solid – Liquid Equilibria

Solid – Liquid equilibria is governed by the principles of thermodynamics and is independent of the scale of measurement and operation.

The ideal solubility of a non-dissociating solute, assuming the effects of pressure and specific heat capacity change on melting are negligible is [7,8]:

$$x_1^{sat} = \exp \frac{\Delta H_{m1}}{R.T_{m1}} \left(\frac{T - T_{m1}}{T} \right) \dots\dots\dots \text{Eq 2.}$$

Where x_1^{sat} is the concentration of solute 1 (mol fraction), dissolved in the liquid phase at the equilibrium temperature, T (K). R is the ideal gas constant (8.314 J.mol⁻¹.K) and ΔH_{m1} and T_{m1} are the enthalpy of melting and temperature of melting for the pure solid phase respectively (J.mol⁻¹) and (K).

Equation 1 implies that solubility is *independent* of solvent type, and is only a function of the equilibrium temperature and characteristic properties of the solid phase. In real systems the effect of non-ideality in the liquid phase can significantly impact the solubility. This effect can be correlated using an activity coefficient (γ) to account for the non-ideal liquid phase interactions between the dissolved solute and solvent molecules. Eq. 1. then becomes [7,8]:

$$\gamma_1.x_1^{sat} = \exp \frac{\Delta H_{m1}}{R.T_{m1}} \left(\frac{T - T_{m1}}{T} \right) \dots\dots\dots \text{Eq 3.}$$

Activity coefficients are known to be a strong function of composition and in most systems, have only a weak dependence on temperature.

2.2.3 Supersaturation

Supersaturation is the driving force for crystallization and is a prerequisite before a solid phase will appear in a saturated solution. Figure 1. shows the situation for a cooling crystallization. At point 1 the system is under saturated and the concentration of dissolved solute is below the solubility curve defined by Eq 3. As the system cools it becomes saturated at point 2 but remains as a metastable liquid phase until the metastable zone is crossed at point 3, where

crystals of the solute will spontaneously form. This process is called nucleation and its kinetic origins are described in the following section.

The width of the metastable zone is system dependent and generally increases as the solute molecules become more complex and flexible. For inorganic salts the metastable zone may be 1 to 2 °C, however in pharmaceutical systems it is typically 20 to 40 °C, and in some instances it can be much larger.

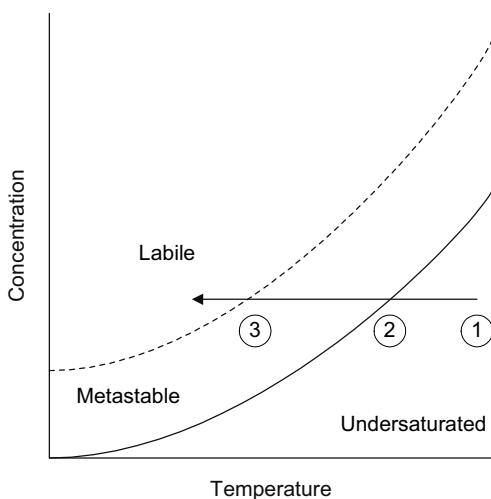


Figure 1: Supersaturation and Metastable Zone Width in a Cooling Crystallization

2.2.4 The Kinetics of Crystallization

2.2.4.1 Primary Nucleation

In the earliest stages of crystal growth when no identifiable solid phase exists, there will be local compositional fluctuations which result in small numbers of solute molecules clustering together as a protonucleus. At this stage the surface area to volume ratio of the nucleus is relatively large and molecules at the surface can't realize the full enthalpy gain available to them at equilibrium; they are partly surrounded by more weakly bound solvent molecules. This situation represents a barrier to crystal growth and at this point the system free energy is minimized by dissolution and break-up of the protonucleus. The effect of entropy is dominant at this point.

Nucleation is defined as the point where the protonucleus is sufficiently large that its surface area to volume ratio exceeds a critical point, and further growth results in a reduction in global free energy; surface effects are now small compared to the inside of the crystal. This is the point where enthalpy dominates over entropy. Subsequent crystal growth and further nucleation events will occur until thermodynamic equilibria is reached, as defined by Eq. 3. The rate of nucleation is defined as the rate at which clusters grow through this critical point.

The critical cluster size and associated free energy barrier have been shown to depend on the degree of supersaturation [5,6] as illustrated in Figure 2. The probability that a protonucleus will reach the critical size and become a stable solid phase depends on the height of the free energy barrier relative to the Boltzman energy distribution of the system. As supersaturation is increased there will eventually come a point where the energy barrier and cluster size are sufficiently small that nucleation is spontaneous. Nucleation will eventually stop when crystal growth has reduced the degree of supersaturation to a sufficiently low level.

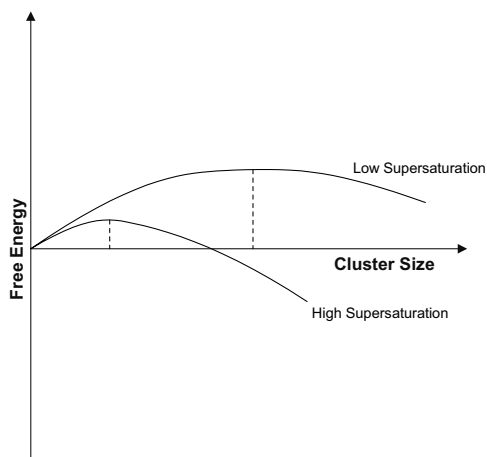


Figure 2: Nucleation and the Effect of Supersaturation.

2.2.4.2 Impurities and Nucleation

The rate of primary nucleation and width of the associated metastable zone are difficult to measure with precision in the laboratory, because of their dependence on environmental factors. Dust particles contaminating a solution, and imperfections on the surface of the crystallizer and agitator are often

responsible for catalysis of the nucleation process, at much lower levels of supersaturation than would be observed in a perfectly clean system. As described above, when water is purified sufficiently and held in pristine glassware it is possible to cool it to -10°C or more without any ice crystals forming. Nucleation can then be promoted by scratching the surface of the glass with a spatula, at which point ice crystals will form and spread throughout the sample. This dependence on trace contaminants and surface properties of the vessel means that primary nucleation is difficult to predict and control during scale-up and scale-down of a crystallization process.

2.2.4.3 *Seeding*

Crystallization processes that rely on primary nucleation are difficult to scale up consistently, because of the issues discussed in section 2.4.2. The addition of small quantities of pre-prepared seed crystals can mitigate this risks. If a small amount of crystalline solid is added to a just saturated solution at point 2 in Figure 1 then the nucleation process is effectively bypassed. The growth of the seed crystals is energetically favorable compared to nucleation. For optimal results the degree of supersaturation must be carefully controlled to match the growth rate of the seed, although in practice this is often difficult to achieve. If the degree of supersaturation exceeds the growth rate of the seed then secondary nucleation will occur. Monitoring supersaturation for the control of crystallization is an active area of research.

2.2.4.4 *Solvent Effects on Nucleation and Growth*

Solvent effects are important to the process of nucleation and crystal growth, although they are not fully understood [9,10]. The type of solvent – solute interaction in the liquid phase is known to impact the kinetics of forming a protonucleus and of subsequent crystal growth. A solvent may coordinate with a flexible solute molecule and present it to the growing nucleus in the optimal configuration for assembly. The solvent may also form hydrogen bonds with functional groups of a solute molecule that are also required in the crystal lattice, thus disrupting the assembly process. The rate of crystal growth after nucleation may be affected by adsorption of solvent molecules onto the crystal surface and subsequent blocking of growth sites. The metastable zone width will be significantly different depending on solvent type and in many instances only certain types of solvent will facilitate the nucleation of a particular solid phase.

In electrolytic systems the crystallization solvent type will affect the degree of solute ionization. This is an important factor in the rate of nucleation and can be successfully utilized for polymorphic control [11].

Solvent selection based on cohesion parameters, like those of Hansen [12], and by multivariate statistical methods like principal components analysis are two potential methods that can be used for solvent selection. These effects will be examined further in section 3.6.1.

2.2.4.5 Secondary nucleation

The presence of a crystalline solid phase in a supersaturated solution often causes new nuclei to form at appreciably lower levels of supersaturation than is required for primary nucleation events. Several mechanisms are responsible for this [6]:

- Shear nucleation caused by flow across a crystal surface.
- Contact nucleation by collision of crystals with the walls of the crystallizer, agitator or neighboring crystals.
- Fragmentation of fragile crystals
- Fines and dust added with a batch of seed crystals.

2.3 Crystal Structure and Polymorphism

2.3.1 Polymorphism

The packing arrangement of atoms or molecules in a crystalline solid phase is generally not unique, and for organic molecules in particular, it is common for two or more crystalline forms of the same substance to exist. The most familiar example in elemental terms is Graphite and Diamond. Both are composed entirely of the element Carbon, however their crystal structures are very different, and so too are their physical properties. Calcium Carbonate is another common example with three polymorphic forms; Calcite, Aragonite and Vaterite.

The term pseudo-polymorph is frequently used to describe the other types of solid phase that are often encountered in the pharmaceutical sector. It includes the crystalline hydrates and solvates together with the amorphous or glass solid state. The structure and properties of these phases will be discussed in section 3.2.

Polymorphs are common in organic chemistry and are prevalent when hydrogen bonding is involved in the crystal lattice. 2,6 di-hydroxybenzoic acid [13] is a well documented example. Polymorphism is more probable when molecules are large and possess conformational flexibility, which increases the number of feasible molecular arrangements that can produce a stable crystal

lattice. These characteristics are common in both synthetic intermediates and API. The drug Cimetidine, which is the subject of the following case study, is currently known to exist in five polymorphic forms with an additional three hydrated forms [14].

Polymorphism is critically important in the design of new drug API [9] and affects a number of areas. The main impact is to the bioavailability and release profile of a drug substance into the body. This is due to differences in solubility and dissolution rate, between the polymorphs. The chemical and physical stability of the formulated drug substance is also dependent on the polymorphic form. Patented registration of all discovered forms and their manufacturing conditions is an important element in protecting a pharmaceutical companies intellectual property.

From a manufacturing perspective the handling characteristics, filtration and drying performance of drug API and intermediates, are significantly affected by crystal shape (morphology) and polymorphic form. Solvent mediated transformation between polymorphs and pseudo-polymorphs can easily occur when washing an isolated solid with a different solvent to that used in crystallization, leading to subsequent handling problems. It should be noted that two polymorphs may have very similar morphology even though their crystal lattices are structurally different.

Because of these issues considerable time and effort are expended in the search for all feasible polymorphic and pseudo-polymorphic forms of a drug substance. Screening tests are conducted early in the development process at the milligram scale, in multi-well plates. The parameters that are important in controlling which polymorph will form are; temperature, solvent or solvent mixture, degree of supersaturation, impurities, time, composition and surface quality of the crystallization vessel. Nucleation may also be affected by solid phase impurities and traces of seed crystals. Polymorph screening is labour intensive and takes significant time and skill to carry out, although automated lab equipment can reduce the burden to a degree.

Polymorphs are usually named in the chronological order of their discovery and in general this has no bearing on their thermodynamic stability. Typical conventions are Form A, B, C.....Form I, II, III.....and Form α , β , γ

2.3.2 *Solvates and Hydrates*

The inclusion of solvent molecules as part of the crystal lattice is another common phenomena in both organic and inorganic systems. Calcium phosphate used in modern building plaster, sets when it reacts with water and crystallizes as a stable deca-hydrate. In pharmaceutical systems it is common

for manufacturing intermediates to be crystallized and isolated as solvates or hydrates. The solid state achieves greater stability by the inclusion of solvent or water molecules in the fundamental motif (building block) of the crystal.

Solvates and hydrates can be unstable when removed from solution, and are not usually desired as the solid form of the final API. The water or solvent molecules often lie along a crystal axis and can diffuse out of the crystal along these channels to achieve equilibrium with the surrounding vapour phase. In some instances this weakens the crystal structure and may cause fragmentation.

2.3.2.1 *The Amorphous Solid State*

A second type of solid phase is also possible, and commonly found in pharmaceutical systems. In this case, molecules in the solid phase are randomly distributed like those of the liquid phase, and do not possess long range order. A solid of this type is called amorphous or glassy, and is often found in organic molecules that have several flexible bonds.

The amorphous phase is not usually a desirable state for the API because the formation process is more random and difficult to control than a crystallization. A second dispersed liquid phase is usually formed just prior to freezing and may coalesce or disperse under the influence of hydrodynamic forces in the crystallizer, making the process sensitive to micro-mixing effects on scale up. Amorphous solids also have significantly lower thermodynamic stability than related crystalline material and may subsequently crystallize during formulation and storage. Because of the non-uniformity of the amorphous solid it can more easily incorporate molecules other than the API, making purification less effective.

2.3.3 *Enantiotropy and Monotropy*

The relative thermodynamic stability and therefore solubility of two polymorphs can take one of two forms, either monotropic or enantiotropic, depending on the relative values of ΔH_m and T_m in Eq. 2 [7,8].

In the monotropic case the relative solubility of the two polymorphs does not change with temperature; if Form I is the most stable and least soluble at low temperatures then it will also be the same at all other temperatures, Figure 3. An example of this behavior is the Cimetidine Form A and B relationship presented in the case study of section 6.

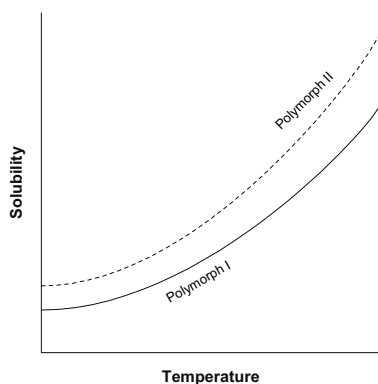


Figure 3: Monotropic behavior between two polymorphs

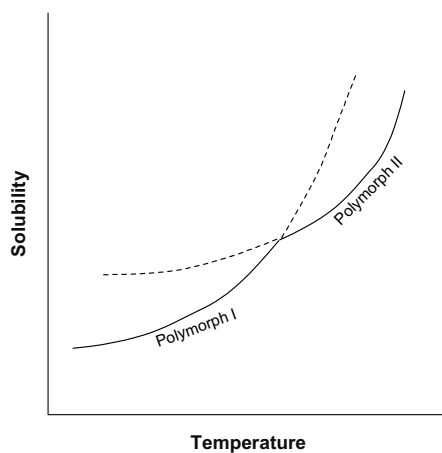


Figure 4: Enantiotropic behavior between two polymorphs

In the enantiotropic case the relative solubility and stability changes at a specific transition temperature where the two solubility curves cross. A given polymorph may be more soluble (less stable) above the transition point, but less soluble below and vice versa, Figure 4. An example of this relationship is the Form C and A or B relationships for Cimetidine in the case study.

The heat of fusion rule of Burger and Ramberger can be used to distinguish each case [9,15]:

Table 1: Heat of Fusion Rule of Burger and Ramberger:

Does the higher melting polymorph have:	Then the system is:
the smaller heat of fusion ?	enantiotropic
the greater heat of fusion ?	monotropic

It is important to understand this behaviour when selecting a crystallization solvent and the operating temperature range for a new process. The temperature range for the crystallization should be selected so that the desired polymorph is always the thermodynamically stable form. If this is not feasible then kinetic studies will be required to confirm that the polymorphic form that crystallizes first is subsequently converted to the desired form during processing. It is also possible that more than two polymorphic forms could be involved in this type of system, increasing its complexity.

2.3.4 Polymorphism and API Product Design

The most thermodynamically stable polymorph is usually desired for the API product to maximize its formulated stability. Selecting the thermodynamically stable form does however, have the disadvantage of minimizing the solubility and bioavailability. Although less desirable and common it is feasible to use an amorphous solid form of the API if it can be demonstrated that it is stable in the formulation.

For many pharmaceutical systems it is not possible to manufacture a stable crystalline form of the pure API for formulation. In these cases the clinical development and formulation teams will investigate a range of standard salt forms by adding an acidic or basic counter ion. Typical examples are sodium salts, fumarates, maleates and HCl salts. The addition of a counter ion to the crystal structure can significantly increase its lattice energy and stability, whilst maintaining good solubility and bioavailability. Salt formulations are estimated to account for half of all the drug molecules administered in therapy [16].

2.3.5 Crystal Structure Prediction

The prediction of crystal structures by “ab initio” quantum mechanical methods, and the identification of stable polymorphic forms and the conditions under which they will crystallize, is of great interest to the pharmaceutical industry. Some progress has been made towards this goal in recent years [17, 18] with a degree of success for small and conformationally simple pharmaceuticals. The methods are still a number of years away from routine use in the day to day research and development environment.

Two techniques are currently being evaluated, based on force field models [17] and density functional theory [18]. Both approaches start by defining a potential crystal motif by calculating and minimizing the forces acting on a single molecule in the vapour phase. A search is then performed on a large number of feasible packing arrangements for each specific conformer to find the most probable, with the smallest lattice energy. These methods currently predict the occurrence of many more polymorphs with similar lattice energies and stabilities than are observed in practice.

2.3.6 *Polymorphism, Nucleation and Growth*

Predicting exactly which polymorph or solvate will appear in a pharmaceutical crystallization process from first principles is not possible at the current time. As a result, a great deal of experimental effort is currently spent in the design of crystallization processes, and whilst fit for purpose there are many that will be sub-optimal as a result. As discussed above, the first difficulty is that of predicting which polymorphic forms are feasible and could occur in the right situation, together with the order of their thermodynamic stability. Polymorph screening experiments are currently used to identify as many forms as possible and to characterize their thermodynamic stability. These will be discussed further in section 4. Even if the thermodynamic stability and structures of all available polymorphs were known, together with the relevant solubility curves to map the equilibrium landscape this is still not sufficient information to design a process, because the kinetics of nucleation and crystal growth must also be understood. Despite these difficulties it is still possible to design and operate robust and effective crystallization processes given adequate time and resource to characterise them by experiment.

2.3.6.1 *Practical Methods for Controlling Polymorphic Form*

The following design options give a flavour for the type of methods that are used to control polymorphic form in the manufacturing environment. There are many combinations of phase equilibria and kinetics that may be observed in practice. Applying the theoretical framework presented so far, and adapting the following control strategies will cover a wide range of situations. It is not feasible however to cover all possible combinations in this short chapter.

The process of crystallization is governed by kinetic and thermodynamic effects. The consideration of both of these is important in controlling the polymorphic form of a product. The available states (polymorphs) that a system may reach are defined by thermodynamics, but it is kinetics that guides the path taken between these states, and control when a given state will be reached in a process. In the time constrained environment of a production plant it is often

kinetics that will determine the end point of a process and not thermodynamic equilibria.

Figure 5. shows the solubility curves for a monotropic system of two polymorphs and will be used to discuss methods for controlling the polymorphic form of the product. In this instance the thermodynamically stable and thus least soluble polymorph is Form I.

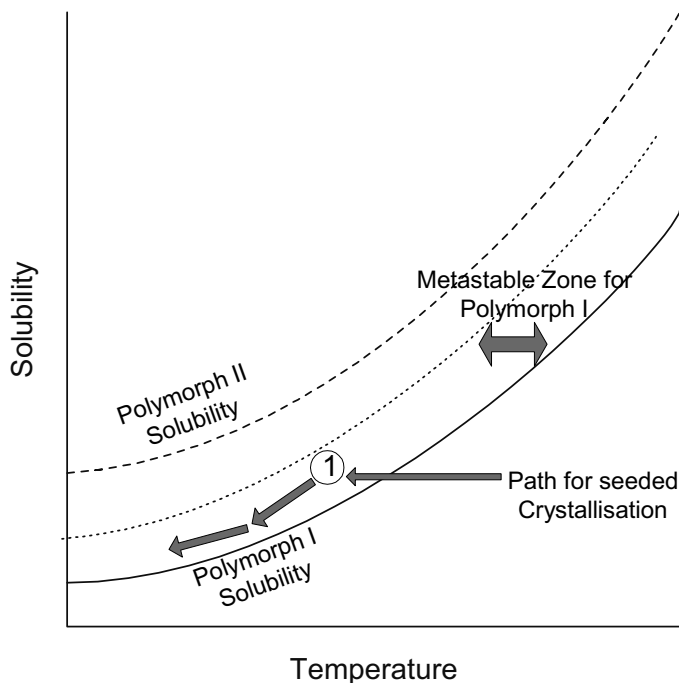


Figure 5: Seeding to Control the Polymorphic Form in a Monotropic System

At point 1, the only form that is supersaturated is Form I, and because supersaturation is a pre-requisite to crystallization it is the only form that could precipitate as a solid phase. If the metastable zone is crossed for Form I before the solubility curve is reached for Form II then Form I will crystallize first and continue to grow unhindered. Unfortunately the width of the metastable zone cannot be predicted theoretically at the present time and is sensitive to physical and chemical impurities and the surface quality of the crystallization vessel. This leads to uncertainty in process scale up.

If seed crystals of Form I are added at point 1 then the process of primary nucleation is avoided and the seed will grow in preference to nucleation. If the

degree of supersaturation is matched to the crystal growth rate, as illustrated by the thick arrows, then a robust and scaleable process will be achieved.

Selecting a solvent with high solubility should help in this instance because the relative solubility of two polymorphs is largely defined by their solid state properties (Eq. 3) and is largely independent of the solvent. This is because the components in the liquid phase are identical for both polymorphs, and the effects of non-ideal solute-solvent interaction will largely cancel out. In solvents where the solubility is high, then the absolute difference in solubility will also be high, and the window for seeding and process control will be greater. This should result in a more robust process.

The rate of nucleation is dependent on the degree of supersaturation as described in section 2.4.1, and because this will always be larger for Form I it may be *incorrectly* assumed that Form I will always precipitate first. The true situation is somewhat more complicated because the critical size, activation energy and nucleation rate also depend on the solid state that is being formed [6]. It is quite feasible and a regular occurrence, that a less stable polymorph will have a higher rate of nucleation than a more stable form, as illustrated in figure 6.

Whenever the solubility curve is crossed for the less stable Form II there is a risk that *it* will nucleate and contaminate the product. This situation is very probable when the solubility curves of the two polymorphs lie close together, as shown in Figure 21 of the Cimetidine case study. The addition of seed crystals of Form I, close to its solubility curve, and minimization of the supersaturation during the growth process is a good method of control in this instance. Solvent selection to extend the width of the Form II metastable zone would also be desired, as discussed in section 2.4.4.

When a less stable polymorph crystallizes first and grows quickly it reduces the degree of supersaturation relative to Form I and may prevent Form I from nucleating at all. The system could remain in this metastable state indefinitely if the energy barrier is sufficiently high and prevents transformation of the solid state from Form I to Form II. Such transformations may be solid state or solution mediated; in the latter case they will generally occur faster in solvents where the solubility is high. Transformation may occur in the solid state after isolation and drying, or during storage if the transition temperature is accessible. Stability trials of the API and formulated product are essential in detecting such changes. In general terms a low temperature will reduce the probability and rate of both forms of transformation.

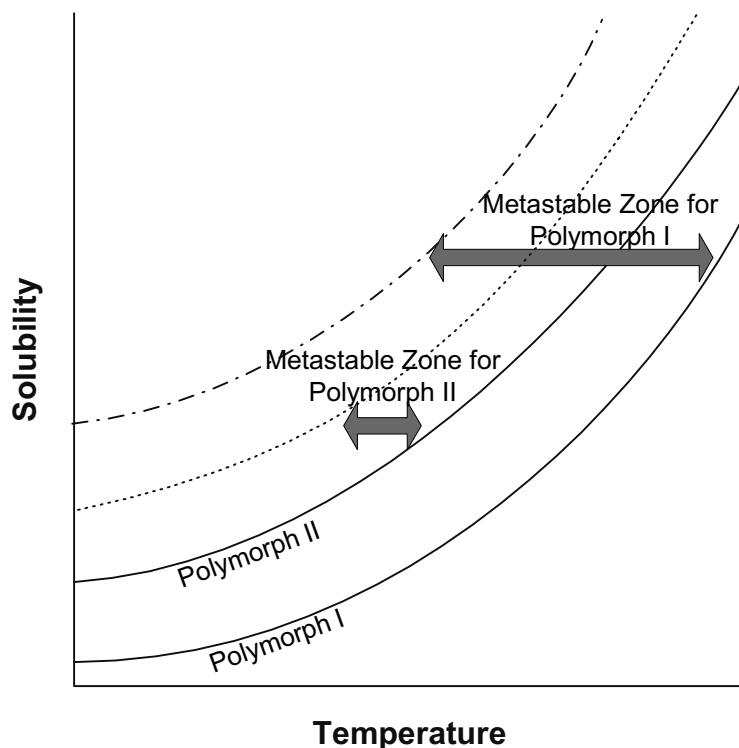


Figure 6: An Example of Overlapping Metastable Zones

There are two important options to consider when designing a process to make a metastable polymorph. If the system is enantiotropic then it may be feasible to operate it in a temperature range in which the desired form is thermodynamically preferred and to use the tactics described above. If this is not possible then kinetic control must be utilized as in the case study on Cimetidine. The system should be moved quickly to the region where both Form II and Form I are supersaturated; if the nucleation rate for Form II is fast then this may be sufficient to cause its precipitation in preference to Form I. The addition of seed crystals of Form II will help to achieve growth of the desired product. Form II should be crystallized as quickly as possible so that the degree of supersaturation is reduced and the probability of nucleating Form I is minimized. This tactic will probably induce secondary nucleation of Form II and may not be conducive to crystal growth, possibly leading to a small average particle size and potential problems in isolation and drying.

The addition of a second miscible solvent, in which the solute has a relatively low solubility (antisolvent) is often used to drive supersaturation. Because this can be done rapidly it is an ideal method for producing a metastable polymorph. Seed crystals could be added to a volume of antisolvent in a batch reactor with agitation to ensure suspension. The solute dissolved in the co-solvent is then added slowly to the vessel [19]. The degree of supersaturation that this method initially generates is extremely high, promoting fast growth of the seed crystals. Towards the end of the addition the co-solvent concentration is high and so too is the solute solubility. This implies that the rate of change of supersaturation with respect to addition rate will be at a minimum at the same time that the solid surface area is at a maximum. Over the entire process this will give the optimal profile for growth of the seed crystals.

As discussed in section 2.4.4 the coordinating ability of a solvent will often affect the rate of nucleation and crystal growth differently between two polymorphs. This can be used as an effective means of process control and information on solvent effects can often be obtained from polymorph screening experiments. There are no theoretical methods available at the present time which accurately predict the effect of solvents on nucleation rates in the industrial environment.

2.3.6.2 A Tale of Disappearing Polymorphs - Ritonavir

The case study of Ritonavir [19] is valuable in highlighting the potential consequence of a previously unknown polymorph appearing in a pharmaceutical product. It has made a far reaching impact on the industry and the thoroughness of polymorph screening.

Ritonavir is a product of Abbott Laboratories Ltd. for the treatment of HIV and is marketed as NorvirTM, in liquid and semisolid capsule formulations. It received FDA approval for market launch in march 1996, at which time only one polymorphic form of Ritonavir (Form I) was known. Two years later in early 1998 a laboratory responsible for testing the formulated product in the US reported dissolution test failures of the semisolid capsules, and noted that drug product had precipitated out of solution. A new polymorphic form had been discovered that was thermodynamically more stable than the existing form and approximately 5 times less soluble in the formulation. Figure 7.

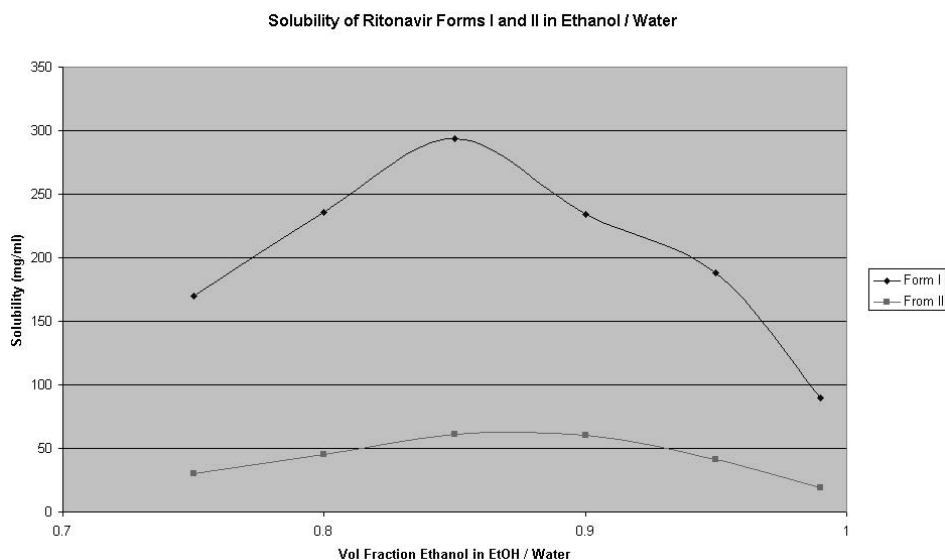


Figure 7: Solubility of Ritonavir Forms I and II in Ethanol / Water mixtures. [16]

Samples of the Form I API were formulated in the laboratory to understand the precipitation issue. It was quickly discovered that the laboratory process now produced material with the same precipitation problems as the capsules from the manufacturing plant. Despite considerable effort the Form II precipitate could not be avoided. It is suspected that the laboratory equipment had become contaminated with trace quantities of the Form II crystals and these promoted the transformation of Form I material into the thermodynamically stable Form II.

During the investigation of this change it was suggested that there was perhaps a quality issue with the API manufacturing plant in Italy, so a contingent from the US were sent to investigate. After their visit it is reported [16] that significant levels of Form II were found in the bulk drug API. This may be coincidental or a result of seed contamination by the visitors. Abbott Laboratories reported marketing issues as stocks of the semisolid formulation ran low. Issues highlighted with the new Form II were dissolution test failures of the formulated product and a change in the morphology of the drug substance which impacted on the crystallization behaviour and caused higher levels of impurities and residual solvent in the API. A reduction in the dissolution rate at the formulation step was also noted.

Abbott Laboratories were forced to rapidly develop a new formulation to accommodate Form II and developed a new seeded crystallization process to

ensure that the bulk drug production process continued to make Form I, with its superior purity and handling characteristics.

Abbott Laboratories incurred additional costs because of the registration issues associated with the new manufacturing and formulation processes. It is a credit to their development staff that these improvements were implemented quickly and without impact on the market. Throughout the industry, loss of API, formulated product and potential sales through polymorphism issues is a significant business concern. Performing thorough but expensive polymorph screening experiments is the only method of minimizing this risk at the present time.

2.4 Designing API Crystallization Processes

The aim of this section is to provide a generic step by step methodology for the design of a final purification process for a non-salt form API using crystallization. The process objective is to consistently manufacture API of the desired purity and polymorphic form, within the constraints of a typical batch production facility. A brief outline of the analytical techniques that may be required is presented in section 4.6.

2.4.1 Step 1 – Polymorph Screening

Polymorph screening experiments should be performed at the milligram scale, in 96 well plates, using protocols [9] that investigate the affects of:

- Temperature
- Solvent composition
- Degree of supersaturation
- Time
- Impurities

The results of the polymorph screening step in combination with bioavailability studies, provide the information required by the clinical research team to nominate the desired crystal form of the API for long term manufacture and formulation. This form will usually be the most stable polymorph, where a number of forms have been identified, or a salt form if bioavailability is low or when there are formulation concerns regarding polymorph stability. In some cases it may be necessary to select an amorphous form or metastable polymorph because of crystallization difficulties, time constraints or bioavailability requirement. The nomination of a hydrate or solvate is generally avoided because of their relative instability and compositional variability; such constraints are less of a concern for the earlier synthetic intermediates.

2.4.2 Step 2 – Polymorph Stability

When a number of polymorphs are identified in step one they should be characterized by Differential Scanning Calorimetry (DSC) to obtain ΔH_m and T_m data. This information confirms their relative stabilities with respect to temperature. If DSC data cannot be obtained then slurry experiments should be performed. It is always good practice to confirm the relative stability with slurry experiments because DSC traces can be difficult to interpret correctly, and can mask subtle effects.

Slurry experiments are a common method of determining which of two polymorphs is thermodynamically more stable. Samples of both polymorphs are added to a solvent and maintained at constant temperature, with agitation, for sufficient time for the stable polymorph to grow at the expense of the less stable form. The final solid form is analysed by X-Ray Powder Diffraction (XRPD) or similar.

Enantiotropic behaviour may constrain the temperature envelope over which a crystallization process could operate. Transition temperatures can be predicted with DSC derived ΔH_m and T_m values together with Eq. 2. Slurry experiments on either side of the transition temperature can then be used to validate the calculations.

2.4.3 Step 3 – Solubility Measurement and Solvent Screening

Once the desired solid state of the API has been chosen it is then necessary to select the crystallization solvent. High throughput solubility measuring equipment is gaining popularity within the industry. It offers an efficient method of generating large quantities of solubility data at different temperatures, and over solvent composition ranges in mixed solvent systems. The equipment works by monitoring the solution turbidity as the temperature is ramped up and then back down to the starting point [20, 21], thus identifying the clear and cloud points for that composition. The clear point is the limit of solubility and the cloud point identified the occurrence of nucleation; this technique determines the solubility curve as well as the metastable zone width. The use of predictive and correlative solubility modelling techniques are relevant to these high throughput systems because they can target the most credible solvents or mixtures to investigate and identify experimental outliers for further scrutiny and solid phase analysis.

Solubility measurements should be made for the desired polymorph in 5 or 6 representative solvents that cover the range of segment types in the NRTL-SAC method, and within the polymorphs stable temperature region where enantiotropy exists. Solubility should be measured in mol or mass fractions and

the solid phase that is in equilibrium at the end of the experiments should be confirmed by XRPD or similar.

The use of thermodynamic models to correlate and predict solubility behaviour in both single solvents and mixtures can be beneficially applied at this point. This technique both validates the experimental data and minimizes the experimental workload for the design of an optimized process. These techniques are discussed further in section 5.

The solubility data can be regressed with the NRTL-SAC model [1] to obtain a set of segment contributions for the solute. This model is then used to predict solubility behaviour in all of the other solvents in the NRTL-SAC database. The solubility data can also be used to fit local UNIFAC group contribution terms using the SoluCalc [4] software. This allows the solubility data to be extrapolated into solvent systems which comprise of the same functional groups. It is also feasible to combine group contribution data from other molecules and thus extend the utility of the model, although with reduced accuracy. Both of these techniques are described through the case study in section 6.

If sufficient data is available from the polymorph screening step to identify solvent types which are likely to promote the formation of the desired polymorph then they can be included in the selection process at this point [12].

2.4.4 Step 4 – Solvent Selection

The selection of a potential list of crystallization solvents is made against the following criteria:

- Chemical compatibility.
- Environmental, Safety and Health impact.
- The maximum boiling temperature of the solvent at atmospheric pressure will limit the maximum operating temperature. (1 atm abs. is the normal operating pressure for most multi purpose plant in the pharmaceutical sector).
- The maximum operating temperature may be constrained by the thermal stability of the API.
- The maximum feasible operating temperature must be a sensible margin below the solvent boiling point, to enable insoluble contaminants to be removed from a pre-dissolved solution of the Crude API, see section 1.1.4.
- The operating temperature may be constrained by enantiotropic behaviour.
- The solubility at the maximum feasible operating temperature should be sufficiently high to achieve the desired volume productivity.
- The final (low) crystallization temperature is limited by the freezing point of the solvent.

- The yield of the crystallization step must achieve acceptable productivity targets.
- If the yield of the crystallization is too high ($> \sim 90\%$) then co-crystallization of impurities is more likely*
- The solvent should be easy to remove through drying and / or washing with a cleaning solvent.

* During the early stages of process development it is very unlikely that relevant impurities will have been synthesized in sufficient quantities that a thorough analysis of their eutectic behaviour can be performed. Eutectics should be investigated when possible and are particularly relevant in the purification of stereo-isomers and in classical resolution using diastereomeric salts [5, 24, 25].

This type of solvent selection problem can be formulated and solved as a Computer Aided Molecular Design (CAMD) problem [22]. Application of this method for solvent selection and design is highlighted in chapter 14 and is not discussed in detail in this chapter. The ProCAMD software [23], which is based on a hybrid CAMD method can be used to solve solvent selection problems of this type.

2.4.5 Step 5 – Crystallization Process Design

The preferred choice for an API crystallization process is a cooling crystallization from a single solvent. This is because temperature and cooling rate are relatively easy to control and to scale up consistently. The decision criteria is based on the solubility profile with temperature and the available yield and productivity.

If the productivity target cannot be achieved then a co-solvent system could be selected using solubility prediction methods like NRTL-SAC [1] and Local UNIFAC [4]. The addition of a second solvent to increase solubility is an effective way of increasing productivity for a sparingly soluble solute.

If the desired yield target cannot be achieved then an antisolvent system can be selected using the same techniques. The antisolvent should be fully miscible with the primary solvent and have a low solubility for the solute. It should be noted that the addition of an antisolvent to reduce solubility and generate supersaturation may introduce scale up issues, caused by the differences in micro-mixing performance between the laboratory and manufacturing plant.

2.4.6 Step 6 – Laboratory Evaluation

Once a set of potential solvents (and antisolvents) have been identified then the solubility behavior should be assessed in the laboratory, confirming the effect of temperature, the isolated solid form and the limits of purification.

Where competing polymorphs may occur it is better to have systems where there is a large difference in the relative solubility of the two forms at the point of nucleation. This enables seeding of the crystallizer with the desired form at a temperature between the two solubility curves. A typical seed loading is 1 to 2 % by weight of the product.

Where a metastable polymorph is required the crystallizer should ideally operate below the supersaturation curve for the more stable form, thus preventing any primary nucleation of the more stable form.

2.4.7 Analytical Techniques for Crystallization Design

The following list identifies the most important analytical techniques that are regularly used in the support of industrial crystallization process development and API solid phase characterization.

2.4.7.1 X-Ray Diffraction (XRD)

This is the gold standard for crystal structure analysis. The diffraction pattern gives a unique fingerprint of the crystal structure. If good quality single crystals of approximately 200 micrometers in size are grown, then an atomic map can be constructed of the crystal lattice. For routine use where speed is important the samples (~50 milligrams) are used in powdered form; such diffraction patterns are usually sufficient to differentiate and positively identify polymorphs. In many instances there is sufficient information available that computer predictions and Monte Carlo simulation can be used to derive the crystal structure, which is valuable when single crystals cannot be made of sufficient size or quality. Diffractograms for Cimetidine Forms A, B and C are presented in Figures 8, 9 and 10 respectively [14].

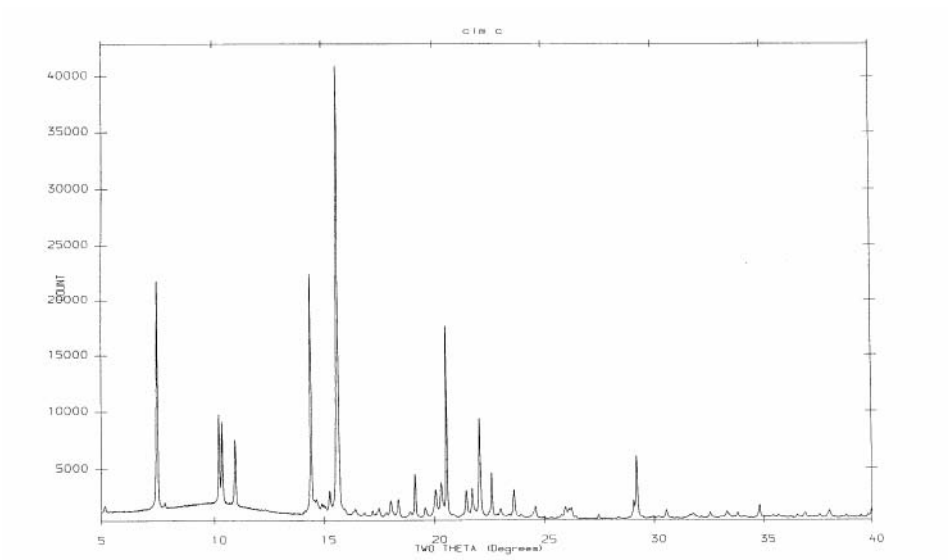


Figure 8: XRPD Spectra for Cimetidine Form A

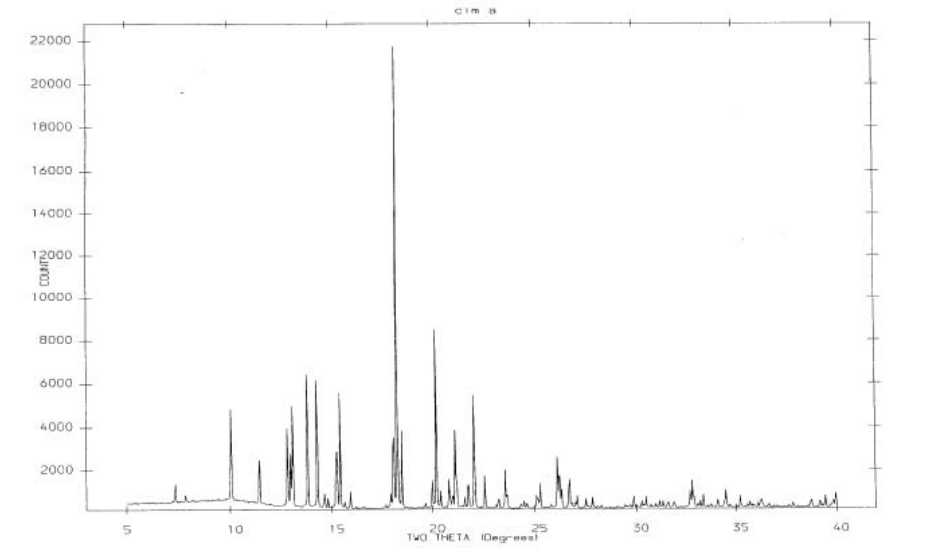


Figure 9: XRPD Spectra for Cimetidine Form B

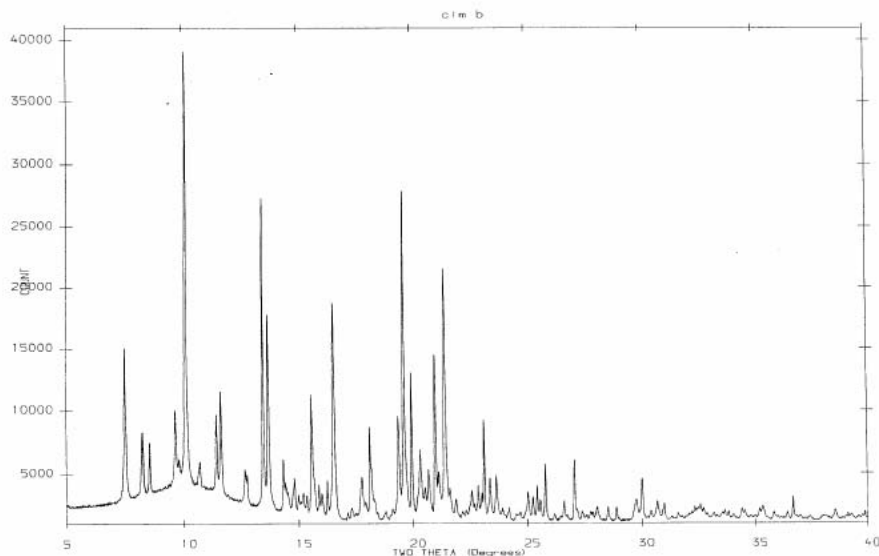


Figure 10: XRPD Spectra for Cimetidine Form C

2.4.7.2 Differential Scanning Calorimetry (DSC)

DSC instruments measure the heat flow into a sample as the temperature is ramped, in comparison to a reference standard. The melting temperature and enthalpy of fusion are quantified. The technique is not suitable for a significant proportion of pharmaceutical compounds because they decompose at the same time as melting. In solvates and hydrates the solvent will evaporate prior to melting which also limits the methods value. Sample size is typically 10 mg.

2.4.7.3 Thermogravimetric Analysis (TGA)

In Thermogravimetric analysis a sample of material is heated at a fixed rate whilst the mass of the sample is continuously recorded. This technique identifies de-hydration, de-solvation and decomposition.

2.4.7.4 Differential Vapour Sorption (DVS)

In Differential vapour sorption a sample of material is placed on an accurate balance in a temperature controlled environment where the humidity of the gas phase can be accurately controlled. The adsorption and desorption behaviour of the sample is quantified with respect to water and hysteresis phenomena are identified.

2.4.7.5 High Pressure Liquid Chromatography (HPLC)

High pressure liquid chromatography is the standard method used to quantify the API and related impurities. It is often used to measure solubility.

2.4.7.6 Nuclear Magnetic Resonance (NMR) Spectroscopy

Nuclear magnetic resonance spectroscopy is often used to quantify the ratio of API and counter-ion in a pharmaceutical salt, together with the type and quantity of hydrate or solvate molecules.

2.4.7.7 Karl-Fischer

Karl-Fischer titration is used to quantify the amount of water in a sample and to assess the degree of hydration.

2.4.7.8 Optical and Electron Microscopy

Microscopy is used to identify crystal morphology and size, and to assess physical form issues like agglomeration and solvent occlusion. It can be used to observe polymorphic transformations in real time with the addition of a hot stage fitting.

The following techniques can be used on-line to monitor batch crystallization processes in real time:

2.4.7.9 Fourier Transform Infra-Red (Ft-IR) Spectroscopy

Near and Mid infrared spectroscopy can be used to monitor crystal form and polymorphic transformations, as well as solution phase concentration.

2.4.7.10 UV-Vis Spectroscopy

Allows the solution phase concentration and degree of supersaturation to be monitored.

2.4.7.11 Raman spectroscopy

Laser excitation causes characteristic photon emissions from the solid phase, identifying polymorphic form and transformation rates. This technique is only suitable for non-fluorescing materials

2.4.7.12 Lasentech Focused Beam Reflectance Microscopy (FBRM)

FBRM provides a real time chord length distribution within the crystallizer. The technique is excellent for determining the onset of nucleation and in following general growth rate and rate transitions associated with polymorphic transformation, reaching equilibrium and attrition effects.

2.5 Solubility Modelling

2.5.1 *Ideal Solubility*

The ideal solubility equation (Eq. 2) is the simplest form of model that is applicable to solvent based crystallization process design. Even though the equation excludes non-ideal interactions in the liquid phase, it is still a useful tool in certain circumstances.

In systems where the liquid phase interaction between the solute and solvent is close to ideal, then Eq. 2 can be used successfully on its own to fit and extrapolate solubility data with respect to temperature. The technique is valuable in an industrial setting, where time pressures are always present. Solubility data points are often available without any additional effort, from initial work on the process chemistry. The relative volume of solvent that is required to dissolve a solute at the highest process temperature in the crystallization is often known, together with the low temperature solubility by analysis of the filtrates. If these data points fit reasonably well to the ideal solubility equation then it can be used to extrapolate the data and predict the available crystallization yield and productivity. This quickly identifies if the process will be acceptable for long term manufacture, and if further solvent selection is necessary.

A primary role of crystallization is to purify the desired product and exclude impurities. Such impurities are frequently related in chemical structure to the desired product, through the mechanisms of competitive reaction and decomposition. Where the impurities are similar in structure it is likely that their interactions with the solvent in the liquid phase will also be similar. In this instance the selectivity of crystallization is mainly attributed to the difference between the respective pure solid phases. The ideal solubility equation can be applied to such systems [5, 8] on a solvent free basis to predict the eutectic composition of the product and its related impurities. The eutectic point is a crystallization boundary and fixes the available yield for a single crystallization step.

The ideal solubility equation has significant value in chiral systems, where a single enantiomer is desired as the product [20]. The behaviour of chiral compounds is very important in biological systems and in drug development, where it is typical for just one enantiomer of an API to be biologically active. The undesired enantiomer may be inert, or possess more serious toxicity effects, as in the case of Thalidomide. Many enantiomeric systems form three discrete solid phases, depending on the solution concentration. Pure crystals of each enantiomer will form at high concentrations of their respective enantiomer. At

similar compositions the crystals may comprise of a 50:50 ratio of the two enantiomers, this is usually referred to as a chiral “compound”. The eutectic composition for the pure enantiomer and the compound can be calculated precisely by the ideal solubility equation, because both individual enantiomers behave identically in the liquid phase. The enthalpy of melting and melting temperature for the pure enantiomer and the conglomerate would be determined from DSC data, section 4.7.2.

2.5.2 The NRTL Segment Activity Coefficient Method

The application of thermodynamic models to the correlation and prediction of pharmaceutical solubility behaviour is an underutilized technique in today’s process research and development environment. This is due to the relatively poor accuracy and limited predictive ability of the previous generation of models. Recent advances in computational chemistry and an increased focus on the life science sectors has led to the development of more appropriate models with significantly improved predictive capabilities. The NRTL-SAC and Local UNIFAC approaches will be discussed here with additional examples given in section 8.

The non-random two-liquid segment activity coefficient model is a recent development of Chen and Song at Aspen Technology, Inc., [1]. It is derived from the polymer NRTL model of Chen [26], which in turn is developed from the original NRTL model of Renon and Prausnitz [27]. The NRTL-SAC model is proposed in support of pharmaceutical and fine chemicals process and product design, for the qualitative tasks of solvent selection and the first approximation of phase equilibrium behavior in vapour liquid and liquid systems, where dissolved or solid phase pharmaceutical solutes are present. The application of NRTL-SAC is demonstrated here with a case study on the active pharmaceutical intermediate Cimetidine, and the design of a suitable crystallization process.

The strength of the NRTL-SAC model in an industrial setting lies in its simplicity and ease of use, together with the rigor of its underlying thermodynamic framework. The model can be driven through Microsoft Excel templates at the data input, regression and calculation stages; making it both easy to use and easy to tailor for local requirements. This accessibility can be used to minimise a company’s reliance on expert property modellers during the early stages of process and product design.

An overview of the NRTL-SAC model will be given here with sufficient detail to understand the case study. Full details of the model and its mathematical formulation are given in [1].

In the NRTL-SAC model a small number of conceptual segments are pre-defined to characterize the prominent interaction mechanisms between molecules in the liquid phase, that account for non-ideal behaviour. These segments are the building blocks from which all of the molecules in the system are composed. Three segments types are pre-defined to represent hydrophobic (X), polar (Y) and hydrophilic (Z) regions on a molecules surface. The hydrophobic segment simulates molecular surfaces with an adversity to form hydrogen bonds. The Polar segment simulates surfaces that are electron pair donating or accepting and the hydrophilic segment simulates surfaces that are hydrogen bond donating or accepting. The strength (or size) of a given segment type in a particular molecule, defines the surface area that is accountable for that segments prescribed mode of interaction. The individual segments are assumed to interact with each other through binary interactions only, and calculated with binary interaction parameters that are *constants* of the model.

The NRTL-SAC description of a molecular in terms of the X,Y and Z conceptual segments is achieved by the regression of a small set of solubility measurements.

The Aspen NRTL-SAC solvent database was identified from the list of solvents presented in the pharmaceutical based International Committee on Harmonization's guidelines for residual solvents in API [28]. Hexane, Acetonitrile and Water were selected as the basis for the X, Y and Z segments respectively, the binary interaction parameters for the segments together with molecular descriptors in terms of X,Y and Z segments were then regressed from experimental vapour-liquid and liquid-liquid equilibrium data from the Dechema database. The list of solvent parameters that were used in the case study are given in Table 13.

The NRTL binary interaction parameters for the X, Y and Z conceptual segments of the NRTL-SAC model, as used in the case study are shown in Table 2.

Table 2: NRTL binary interaction parameters for NRTL-SAC conceptual segments

Segment 1	X	X	Y-	Y+	X
Segment 2	Y-	Z	Z	Z	Y+
τ_{12}	1.643	6.547	-2.000	2.000	1.643
τ_{21}	1.834	10.949	1.787	1.787	1.834
$\alpha_{12} = \alpha_{21}$	0.2	0.2	0.3	0.3	0.2

Ideal solution behavior is assumed for the Y- and Y+ polar segments, i.e. $\tau_{12} = \tau_{21} = 0$

2.5.3 The Local UNIFAC Approach

In contrast to the NRTL-SAC model, the UNIFAC model developed by Fredenslund et. al. [29] divides each molecule into a set of *functional groups* that interact with each other on a binary basis and whose interactions are combined together to describe the global liquid phase interaction between molecules. Because the segments in UNIFAC are based on functional groups it is possible to model a system provided that all of the molecular structures are known. The problem with pharmaceutical sized molecules is that existing UNIFAC parameter tables do not contain many of the group interaction parameters that are necessary, and even when they do, the interactions are fitted to a database of chemicals that are much smaller and simpler than pharmaceuticals, and typically fail to represent them adequately.

An approach based on user defined and fitted UNIFAC group contributions has been presented [30]. Such UNIFAC based methods may ultimately give higher accuracy predictions of phase equilibria, but their cost is significantly higher in time, effort and the experience necessary to build and maintain the relatively complex property database. In many pharmaceutical companies there is no historical database from which to build such models because accurate solubility determination of compounds across a range of different solvents has not been necessary during traditional development process; qualitative measurements and the rule of thumb that like dissolves like have generally been used.

A more efficient and flexible local UNIFAC approach has been proposed through the SoluCalc toolbox in ICAS [4]. Here, the problem of limited solubility data has been resolved by fitting only the most sensitive group interaction parameters. The problem of size and complexity of the API molecules (solutes) has been addressed by representing them with higher-order groups, which are obtained by combining the smaller first-order groups. The price for this improved accuracy is that the local UNIFAC model has a smaller range of predictive ability than for a first-order UNIFAC approach.

Once the local parameters have been fitted to a limited set of data then solubilities can be calculated in a representative set of solvents. Plotting the experimental and predicted data against the Hildebrand solubility parameter of the solvent gives a very good indication of behaviour with solvent type, figure 19. The application of the SoluCalc method to Cimetidine is briefly presented in Section 6.

2.6 Case Study – Solubility Modelling and Crystallization Process Design for Cimetidine

Cimetidine is the active ingredient of the brand Tagamet and is prescribed as a treatment for excessive stomach acid in conditions such as peptic ulcers. The drug acts on the Histamine-2 receptors of the acid producing cells of the stomach lining and represents one of the first examples of receptor targeted drug development in the pharmaceutical industry. Cimetidine is formulated in tablet, syrup and injectable forms; that latter two use Cimetidine Hydrochloride as the active ingredient.

Cimetidine is known to crystallize in 5 polymorphic forms and 3 hydrated forms [11]. Solubility data is presented in this reference for Forms A, B and C. Form E was not known at the start of the study in reference [11] and Form D could not be crystallized, suggesting that it is less stable than the other forms. This is confirmed by melting point data which indicates the order of thermodynamic stability close to the melting temperature is $E < D < A < B < C$, where C is the most stable. The enthalpy of fusion and melting point data for the evaluated forms are presented in Table 3. Form A is the commercially available Form and the desired product for this case study.

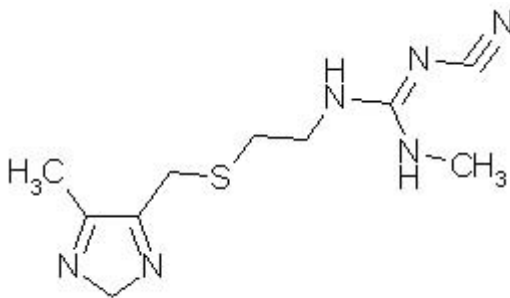


Figure 11: The molecular structure of Cimetidine

Table 3: Physical Properties of Cimetidine Forms A,B and C [11]

Property	Units	Form A	Form B	Form C	Predicted
Melting temperature	$^{\circ}\text{C}$	140.35	140.55	144.35	161.2
Enthalpy of melting (ΔH_m)	J.g^{-1}	174.5	174.7	170.9	199.2
	J.mol^{-1}	44033	44084	43125	
Entropy of melting (ΔS_m)	$\text{J.mol}^{-1}\text{.K}^{-1}$	106.5	106.6	103.3	121.0
Molecular Weight (Mw)	g.mol^{-1}	252.34			
Molecular Formulae		$\text{C}_{10}\text{H}_{16}\text{N}_6\text{S}$			
Smiles String		<chem>N#CN=C(NC)NCCSCC1=NCN=C1C</chem>			

The predicted values in Table 3 were calculated using the group contribution based method of J. Marrero and R. Gani using the ProPred component of the ICAS toolbox [31].

Applying the rule of Burger and Ramberger described in Section 3.3 indicates that Form C is related enantiotropically to forms A and B, and because it is the higher melting form it will also be the most stable at high temperature and thus least stable at low temperature. Applying the same rule shows that Forms A and B are related monotropically to Form B, which is the most thermodynamically stable at all temperatures below the melting point.

Figures 12 and 13 show images of the crystal structures of Cimetidine Form A, derived from X-Ray diffraction data. They were obtained from the Cambridge Structural Database (Ref. CIMETD02) and were visualized using the software package Mercury 1.4 which can be obtained from the Cambridge Crystallographic Data Centre. The figures show a view down the c-axis of the crystal, indicating that Form A has an intermolecular hydrogen bond between the imidazole group and one of the amine groups. The structure shows extensive hydrogen bonding in all directions.

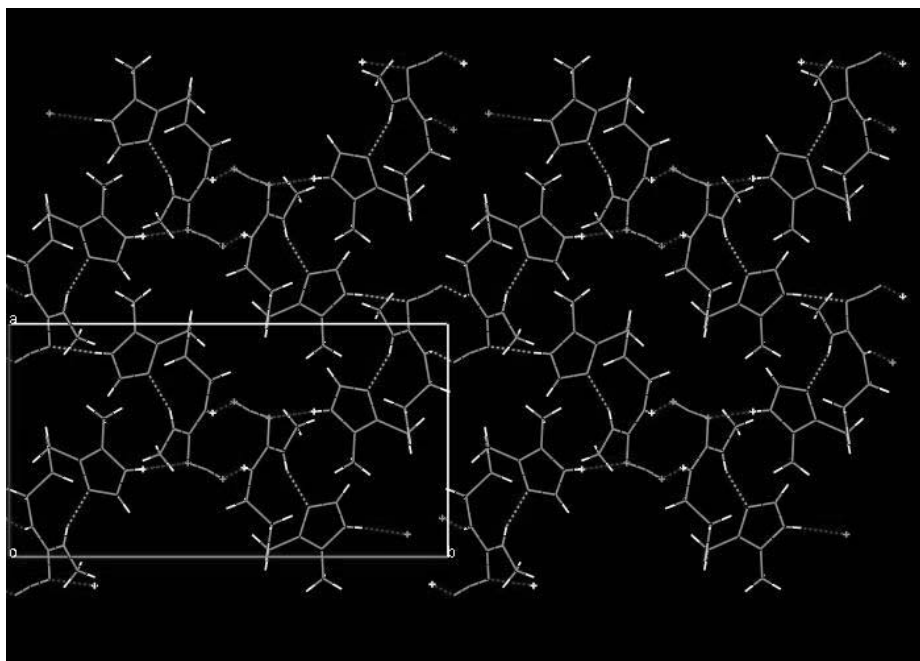


Figure 12: Molecular configuration of Cimetidine Form A showing hydrogen bond locations. Produced by R. Roberts of AstraZeneca. © The Cambridge Crystallographic Data Centre.

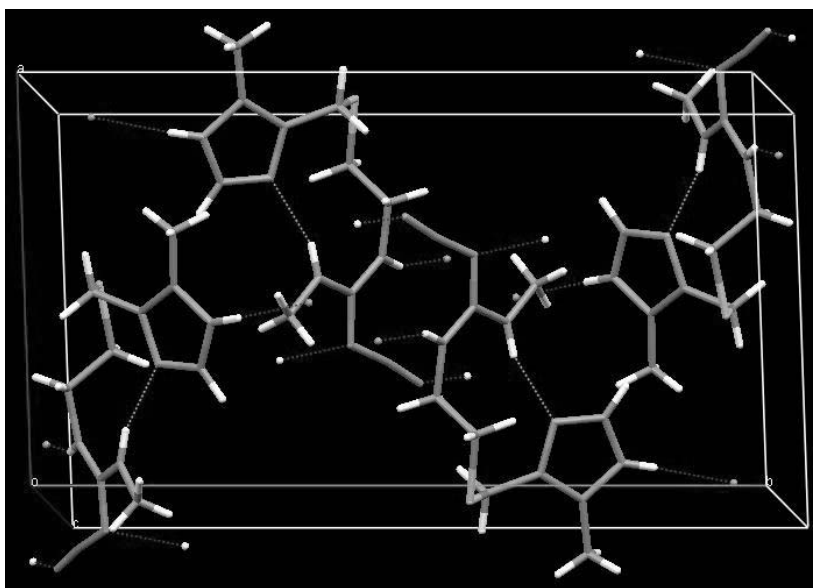


Figure 13: Magnified image from Figure 12. Produced by R. Roberts of AstraZeneca. © The Cambridge Crystallographic Data Centre.

2.6.1 Using the NRTL-SAC model in Aspen Properties

The first step in building a solubility model in Aspen Properties is to define the solute as a new component in two instances, one for the solid phase and the other for the liquid phase. Acetylsalicylic acid is used as a convenient basis for new drug molecules in the Aspen template, because it includes data for all of the necessary thermodynamic methods to satisfy the simulation engine and avoid run time errors.

The NRTL-SAC model was first published in 2004 [1] and is still being developed by the authors. The parameter tables are likely to change as new equilibrium data and solvents are added to improve its accuracy and functionality. The solvent parameters and binary interaction values used in this example are given in Tables 2 and 13.

The Aspen Properties implementation of the NRTL-SAC method is available as a template *.aprbkp file to license holders of Aspen Properties or Aspen Plus release 12.1 or above, by contacting Aspen's support centre or regional sales offices. The template is distributed with an Excel interface to simplify the data regression process and is suitable for non-expert users of Aspen Properties. Numerous Excel templates are available for data analysis and design calculations, based on the NRTL-SAC model.

Solid – Liquid equilibria is represented in Aspen Properties 2004 by the solubility product function, located in the Chemistry folder and defined as follows:

For the equilibrium reaction: Solid \rightleftharpoons Dissolved Solid

The solubility product K_{sp} is defined by:

$$K_{sp} = \frac{[DissolvedSolid]}{[Solid]}$$

where terms in square brackets represent concentrations.

Assuming that the solid phase is pure, i.e. there are no solid solutions present, then $[Solid] = 1$ and

$$K_{sp} = [DissolvedSolid] = x_1^{sat}$$

In Aspen Properties the default equation for K_{sp} is:

$$\ln(K_{sp}) = A + \frac{B}{T} + C.\ln T + D.T$$

.....Eq 4.

Where *A*, *B*, *C* and *D* are constants.

Comparing Eq. 4 with the ideal solubility equation, Eq. 2 shows that:

$$K_{sp}A = \frac{\Delta H_m}{R.T_m} \equiv \frac{\Delta S_m}{R}$$

and

$$K_{sp}B = -\frac{\Delta H_m}{R} \equiv -\frac{\Delta S_m.T_m}{R}$$

and for the case of Cimetidine Form A, *KspA* = 12.81 and *KspB* = -5296.

The following solute parameters in Table 4. are the only ones that are actually used in the NRTL-SAC solubility model.

Table 4: NRTL-SAC Model Parameters For Cimetidine Form A

Aspen Properties Reference	Description	Value
NRTLXY X-R	X	0.328
NRTLXY Y-R	Y-	0.0
NRTLXY Y+R	Y+	0.0
NRTLXY Z-R	Z	1.562
K-SALT 1 (KspA)	Solubility Product constant – KspA	12.81
K-SALT 2 (KspB)	Solubility product constant – KspB	-5296
Mw	Molecular Weight	252.34

The first five parameters may be regressed against experimental data, however, only parameters that are found in the Property / Parameters folder will be updated automatically at the end of a regression. The *K_{sp}A* parameter should be updated manually; this task is done automatically by the Microsoft Excel Template.

The solubility of Cimetidine in a range of pure and mixed solvents is presented in [14]. Cimetidine was obtained commercially from the Aldrich Chemical Company and concentration measurements were generally made by UV-vis spectrophotometry, unless samples had very low solubility in which case the analysis was performed by high pressure liquid chromatography (HPLC). All measurements were compared to a USP reference standard of Cimetidine, obtained from the U.S. Pharmacopoeial Convention Inc. The raw solubility data are presented in Tables 10. and 11. in units of milligrams of solute per milliliter of solution. All solid phase material was identified by FT-IR analysis before use and at the end of the equilibration period, after isolation and drying. The validity of the FT-IR method was confirmed against XRPD analysis and samples of Forms A,B and C. Form D could not be prepared using any of the prescribed literature methods. Form E was not discovered until after the experimental work had been completed.

Before the raw data can be fitted to a thermodynamic model it must first be converted into mass or mole fractions. This operation can be accomplished quickly using a Microsoft Excel spreadsheet that is linked to the Aspen *.aprbkp file; in order to obtain the solvent molecular weights and temperature dependent densities. The molar volume of Form A Cimetidine is also required for this conversion, however, as is often the case it was not available so a density of 1 g/ml has been assumed.

It is recommended that concentration measurements for this type of modeling work are based on analytical standards of mole or mass fraction, to avoid the conversion error caused by density effects. The excess solid phase should always be characterized by a suitable analytical technique, before and after the equilibrium solubility measurements, to confirm that the polymorphic form is unchanged. It should be noted that the crystal shape (habit) does not always change significantly between different polymorphic forms, and visual assessments can be misleading.

2.6.2 Cimetidine Results for NRTL-SAC

Two regression cases have been run on the Cimetidine data, the first uses all of the data points, whilst the second uses a sub-set of the data, to confirm the predictive power of the model. The reduced data set consists of the single solvents in Table 5. which adequately cover the range of conceptual segment types. Where solubility data is supplied in mixed solvents it is necessary to enter the data directly into the Aspen Properties interface before regression.

Table 5: Solvents Used in the Small Regression Case

Solvent	Segment Classes
Dichloromethane	Polar
Water	Hydrophilic
Acetonitrile	Polar
Ethanol	Hydrophobic + Hydrophilic
Heptane*	Hydrophobic
Acetone	Polar

* Actual solubility measurement is for Octane, but not available in the NRTL-SAC database.

The Aspen Properties regression algorithm requires standard deviations for all input data. Datasets that are used with the NRTL-SAC model are minimalist by nature and the assignment of standard deviations is thus somewhat subjective. For this case study the temperature measurements (all 25°C) are assumed to be precise and the concentration measurements are assigned the sample standard deviations given in Tables 10. and 11. These standard deviations do not necessarily take full account for the accuracy of the HPLC method and standards preparation throughout the concentration range of interest, however they are calculable and not subjective. Aspen Technology recommend default standard deviations of 1°C on temperature measurements and a sliding scale of 10% for concentrations of ~ 0.1 mass fraction, and 20% for ~ 0.01 mass fraction etc.. These can be used in situations where the datasets are too small to determine a representative standard deviation.

The regressions were initially run with all five adjustable parameters included; X, Y-, Y+, Z and $K_{sp}A$. It was noted that the regressed value of $K_{sp}A$ was very close to the ideal value (as expected) therefore $K_{sp}A$ was excluded. The standard deviations on the Y- and Y+ terms were found to be relatively large indicating that the model is either insensitive to these parameters or that there is insufficient experimental data to determine them accurately; as a rule of thumb the standard deviation of a regressed parameter should be $\leq 10\%$ of the parameter value if the parameter is significant. In the final regression the Y- and Y+ terms were excluded and set to zero to eliminate their affect. The data for Diethyl ether was found to be a significant outlier and was not used in either of the regression cases. The fitted parameters for both regression cases are given in Table 6.

Table 6: Cimetidine Regression Results for NRTL-SAC

Parameter	All data points regressed	Small regression
X	0.328 (15%)	0.369 (9.2%)
Y-	0	0
Y+	0	0
Z	1.562 (10%)	1.377 (11.5%)
$K_{sp}A$	12.81	12.81
Weighted Sum of Squares	9617	205.4
RMS error	23.11	7.17

Figures in brackets are the % standard deviations for the parameters.

The regression results for both cases are presented graphically in Figures 14. and 15. and in Table 7.

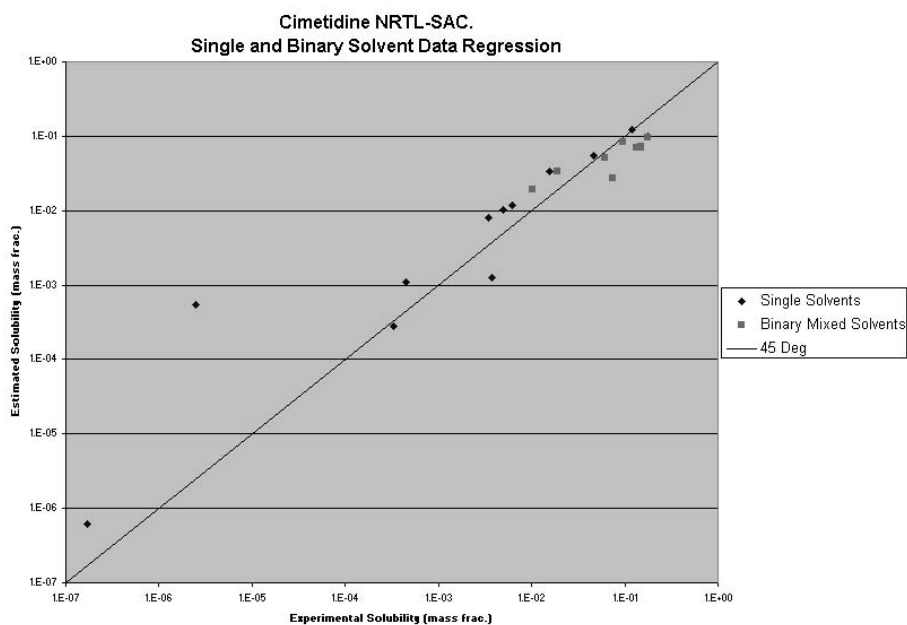


Figure 14: Experimental vs. Estimated solubility (mass fraction) for full regression case

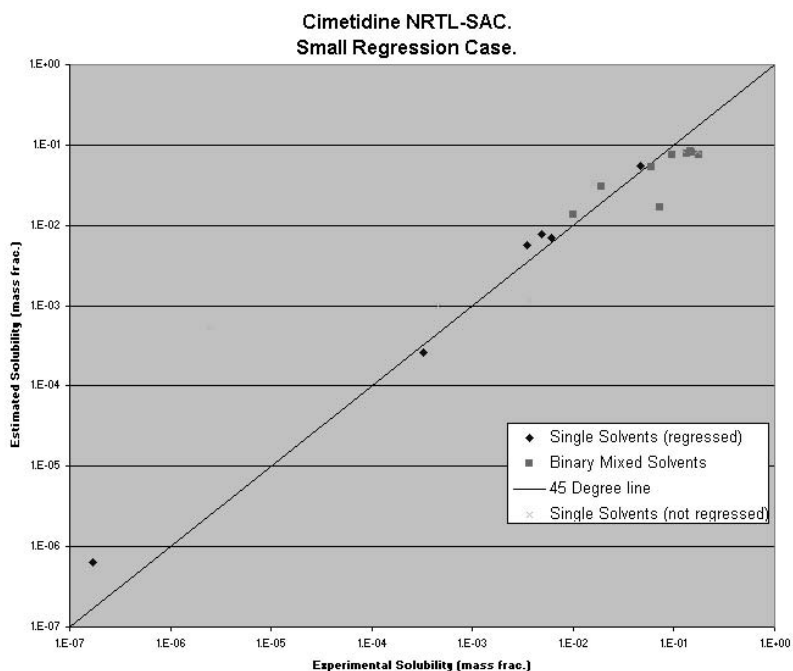


Figure 15: Experimental vs. Estimated solubility (mass fraction) for small regression case

Table 7: Regression Results for Cimetidine with NRTL-SAC

Solvent	All Data Included in the Regression			First 6 Solvents in the Regression	
	Expt. [11] (mass frac.)	Estimated (mass frac.)	% Error	Estimated (mass frac.)	% Error
Dichloromethane	3.26E-4	2.75E-4	-15	2.62E-4	-20
Water	6.11E-3	1.19E-2	95	6.95E-3	14
Acetonitrile	3.44E-3	8.04E-3	134	5.73E-3	67
Ethanol	4.69E-2	5.46E-2	16	5.48E-2	17
Heptane*	1.72E-7	6.12E-7	256	6.40E-7	272
Acetone	4.89E-3	1.02E-2	109	7.85E-3	61
Ethyl Acetate	4.52E-4	1.10E-3	144	9.91E-4	119
Ethylene Glycol	1.19E-1	1.21E-1	1.5	8.76E-2	-26
Diethyl Ether	2.46E-6	5.51E-4	22293	5.41E-4	21890
Methanol	1.75E-1	1.01E-1	-42	8.22E-2	-53
MEK	3.70E-3	1.27E-3	-66	1.19E-3	-68
Isopropyl alcohol	1.58E-2	3.34E-2	112	3.42E-2	117
80% v/v Ethanol / Water	0.1482	0.0713	-52	0.0800	-46
75% v/v Ethanol / Water	0.1476	0.0726	-51	0.0822	-44

60% v/v Ethanol / Water	0.1349	0.0692	-49	0.0779	-42
40% v/v Ethanol / Water	0.0604	0.0514	-15	0.0526	-13
25% v/v Ethanol / Water	0.0191	0.0341	79	0.030	57
10% v/v Ethanol / Water	0.0101	0.0192	89	0.0135	33
50% v/v Ethanol / Methanol	0.0955	0.0834	-14	0.0742	-22
50% v/v Ethylene glycol / Methanol	0.1752	0.0974	-44	0.0758	-57
75% v/v Ethylene glycol / Water	0.0734	0.0276	-62	0.0170	-77

* Actual solubility measurement is for Octane, but not available in the NRTL-SAC database.

The solubility behaviour of Cimetidine in Ethanol / Water mixtures is highly non-ideal. Figures 16. and 17. show that the NRTL-SAC model is capable of representing the general solubility trend and the region of solvent composition where the maximum solubility is likely to be achieved. The results are comparable for both the full regression case, using the binary ethanol / water data, and the small regression case which uses only pure ethanol and water solubility data.

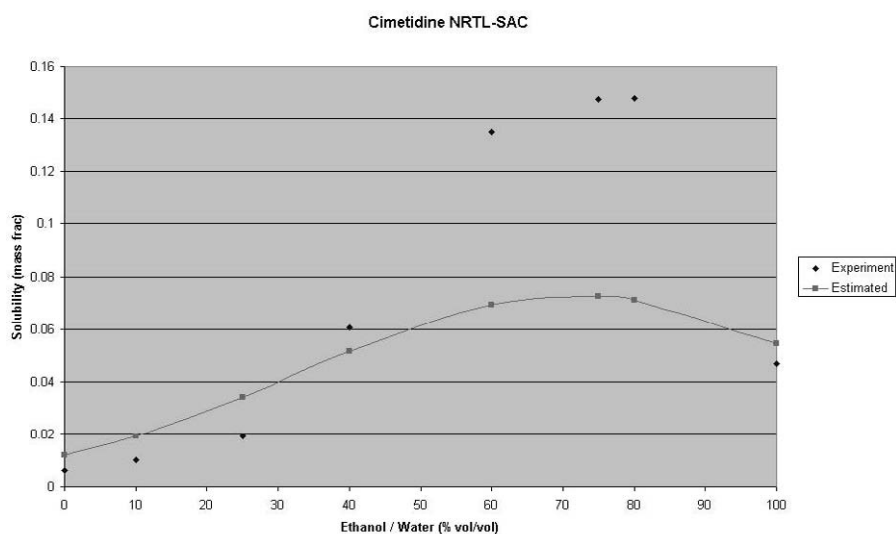


Figure 16: Experimental and Estimated solubility of Cimetidine in Ethanol / Water for the full regression case.

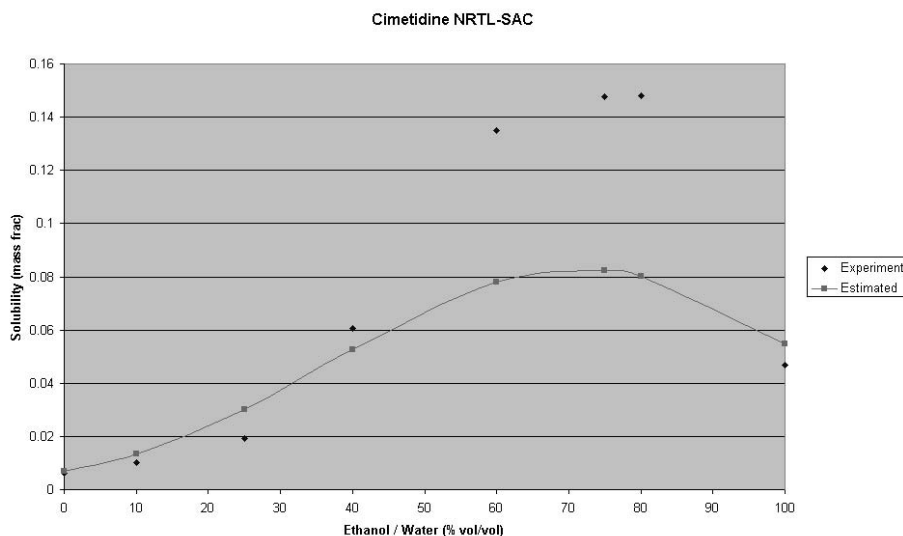


Figure 17: Experimental and Estimated solubility of Cimetidine in Ethanol / Water for the small regression case

A predicted solubility curve for Cimetidine in Ethanol is shown in Figure 18. The affect of temperature on solubility occurs through two mechanisms; the ideal solubility effect (Eq. 3), and the temperature dependence of the activity coefficient, γ . The second affect is not correlated by the NRTL-SAC model, however it is generally accepted that in most phase equilibria problems the affect of temperature on the activity coefficient is relatively small compared to the affect on ideal solubility. A further degree of caution should be applied when extrapolating in this manner, until experimental data are collected.

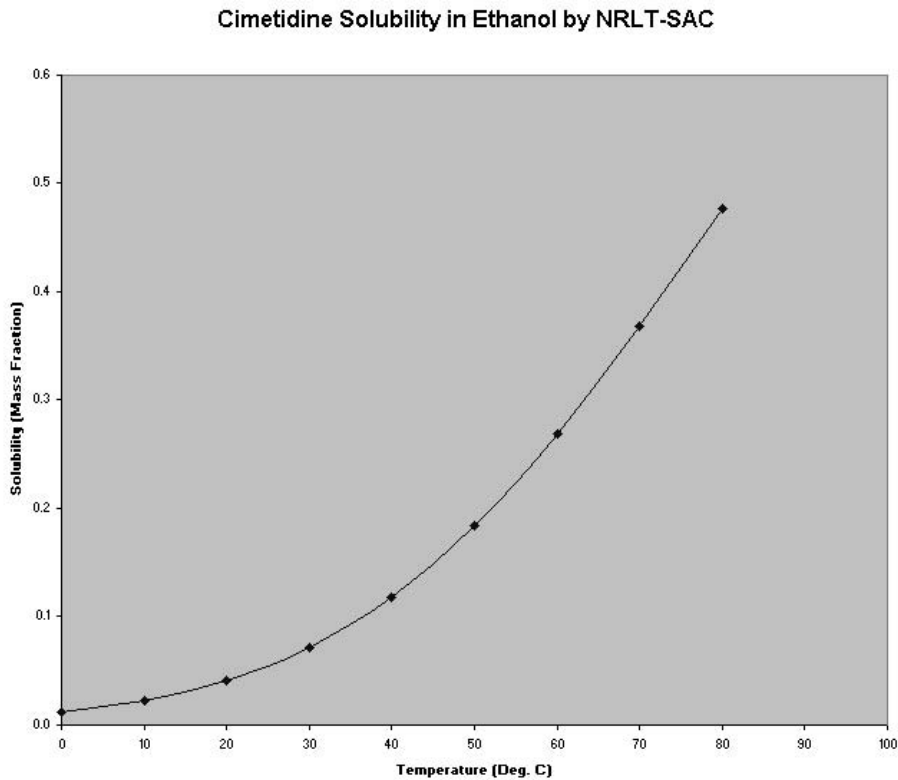


Figure 18: Predicted solubility curve for Cimetidine in Ethanol, full regression case.

Solubility predictions in the full Aspen NRTL-SAC database at 25oC are presented in Table 8.

Table 8: Solubility Predictions for Cimetidine at 25°C
in the Aspen Technology NRTL-SAC Database 2004.

Solvent	Solubility (Mass Fraction)	*Solubility (mg/ml of solution)
ACETIC-ACID	9.79E-02	101.64
ACETONE	1.02E-02	8.07
ACETONITRILE	8.04E-03	6.26
METHYL-PHENYL-ETHER	1.02E-06	1.01E-03
BENZENE	2.26E-05	0.020
N-BUTANOL	2.08E-02	16.80
2-BUTANOL	3.02E-02	24.47
N-BUTYL-ACETATE	5.75E-04	0.50
METHYL-TERT-BUTYL-ETHER	1.85E-03	1.36
CARBON-TETRACHLORIDE	4.90E-06	0.01
CHLOROBENZENE	3.33E-05	0.04
CHLOROFORM	6.35E-05	0.09
ISOPROPYLBENZENE	1.64E-05	0.014
CYCLOHEXANE	9.85E-07	7.62E-04
1,2-DICHLOROETHANE	1.63E-04	0.20
1,1-DICHLOROETHYLENE	3.03E-05	0.04
CIS-1,2-DICHLOROETHYLENE	3.17E-04	0.40
DICHLOROMETHANE	2.75E-04	0.36
1,2-DIMETHOXYETHANE	5.89E-03	5.07
N,N-DIMETHYLACETAMIDE	1.25E-01	117.97
N,N-DIMETHYLFORMAMIDE	8.96E-02	85.03
DIMETHYL-SULFOXIDE	1.97E-01	212.07
1,4-DIOXANE	7.51E-03	7.73
ETHANOL	5.46E-02	43.40
2-ETHOXYETHANOL	1.17E-01	109.26
ETHYL-ACETATE	1.10E-03	0.99
ETHYLENE-GLYCOL	1.21E-01	132.23
DIETHYL-ETHER	5.51E-04	0.39
ETHYL-FORMATE	3.77E-04	0.35
FORMAMIDE	4.88E-02	54.77
FORMIC-ACID	2.71E-01	310.52
N-HEPTANE	6.12E-07	4.17E-04
N-HEXANE	8.58E-07	5.63E-04

ISOBUTYL-ACETATE	1.22E-06	1.06E-03
ISOPROPYL-ACETATE	2.09E-03	1.81
METHANOL	1.01E-01	81.31
2-METHOXYETHANOL	2.54E-02	24.45
METHYL-ACETATE	4.45E-04	0.41
3-METHYL-1-BUTANOL	4.28E-03	3.46
2-HEXANONE	3.40E-03	2.74
METHYLCYCLOHEXANE	6.17E-06	4.72E-03
METHYL-ETHYL-KETONE	1.26E-03	1.01
METHYL-ISOBUTYL-KETONE	3.40E-03	2.71
ISOBUTANOL	1.32E-02	10.59
N-METHYL-2-PYRROLIDONE	6.43E-02	65.92
NITROMETHANE	6.08E-04	0.69
N-PENTANE	1.14E-06	7.10E-04
1-PENTANOL	1.14E-02	9.26
1-PROPANOL	2.86E-02	23.00
ISOPROPYL-ALCOHOL	3.34E-02	26.35
N-PROPYL-ACETATE	1.59E-03	1.40
PYRIDINE	5.23E-02	51.24
SULFOLANE	2.66E-02	33.40
TETRAHYDROFURFURYL-ALCOHOL	2.59E-03	2.28
1,2,3,4-TETRAHYDRONAPHTHALENE	6.82E-02	66.14
TOLUENE	3.70E-05	0.03
1,1,1-TRICHLOROETHANE	3.01E-05	0.04
TRICHLOROETHYLENE	4.50E-02	64.25
M-XYLENE	4.98E-05	0.04
WATER	1.19E-02	11.85
TRIETHYLAMINE	2.65E-03	1.92
1-OCTANOL	1.78E-03	1.46

*The density of Cimetidine is assumed to be 1 g/ml

2.6.3 Cimetidine solubility study with SoluCalc

First a database of solute-solvent properties are created in SoluCalc. The database needs the melting point, the enthalpy of fusion and the Hildebrand solubility parameter of the solute (Cimetidine) and the solvents for which solubility data is available. Using the available data, SoluCalc first prepares a list of the most sensitive group interactions and fits sequentially, the solubility data for the minimum set of group interaction parameters that best represent the total data set. For a small set of solvents, the fitted values from SoluCalc are shown in Table 9. It can be noted that while the correlation is very good, the local model is more like a UNIQUAC model than a group contribution model

(since in most cases a single group is representing the interaction of the whole molecule). Once the local UNIFAC model is obtained, the next step is to create the solubility versus solubility parameter of solvent plot to identify the best solvent candidates (see Figure 19). From figure 19, it can be noted that the best solvents are the lower alcohols (methanol, ethanol, isopropanol). The final step is to use the information to set-up a solvent search problem through ProCAMD (also available in the ICAS package) to verify the solvents and to prepare the SLE-phase diagrams that can be used for crystallizer design calculations. Figure 20 shows the results of the solvent search with ProCamd. It can be noted that ethanol has been found to be a suitable solvent candidate.

Table 9: Correlated Solubility Values From SoluCalc

Solvent	Solubility (moles solute / moles solvent)		Error (%)
	Experimental [11]	Predicted	
Methanol	0.02560	0.00256	-90
Ethanol	0.00883	0.00883	0
Isopropanol	0.00640	0.00937	46
Acetone	0.00113	0.00113	0
Ethyl Acetate	0.00016	0.000158	-1.25
Methyl Ethyl Ketone	0.00106	0.00980	824
Water	0.00607	0.00607	0

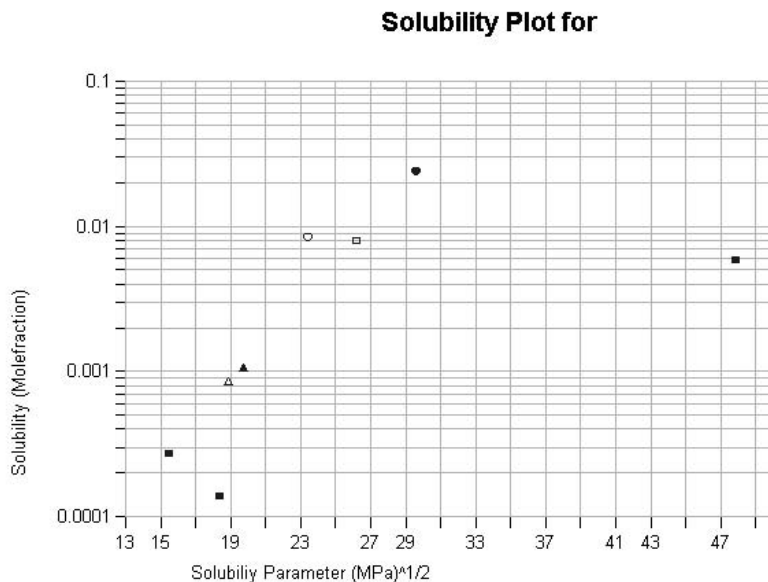


Figure 19: Plot of calculated solubilities versus solubility parameter of solvents.

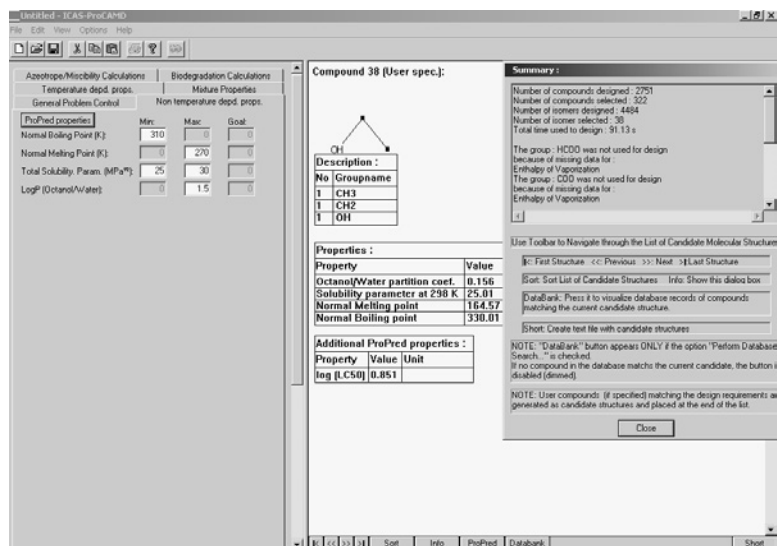


Figure 20: Generation of solvent candidates through ProCAMD based on the solubility analysis with SoluCalc.

2.7 Cimetidine Crystallization Process Design with NRTL-SAC.

The procedure described in section 4 will now be applied to the case of Cimetidine, using the NRTL-SAC model of the full regression case presented in section 6.2. The following screening calculations were built into a Microsoft Excel spreadsheet, using the Aspen – Excel interface to calculate the solubility data.

For each solvent, or row in the spreadsheet:

1. The Normal boiling point is read in from the Aspen interface.
2. The maximum solvent operating temperature is calculated as the boiling temperature minus a 15°C safety margin, to prevent product crystallization and blockage when screening (filtering) between the dissolver and crystallizer. Section 1.1.4.
3. It is assumed that the maximum permissible operating temperature is 90°C, and above this the API would decompose, giving rise to an unacceptable level of impurity.
4. The maximum feasible operating temperature is derived from steps 2 and 3
5. The maximum solubility is calculated by NRTL-SAC in mg/ml solution = x_{hi}
6. The Normal freezing point is read in from the Aspen interface.
7. A minimum approach temperature to the solvent freezing point is defined.
8. A minimum desired operating temperature is defined to match the crystallization and isolation equipment's normal operating temperature.
9. The minimum feasible operating temperature is derived from steps 7 and 8
10. The minimum solubility is calculated by NRTL-SAC in mg/ml solution = x_{lo}
11. The theoretical yield is calculated $= (x_{hi} - x_{lo}) / x_{hi} * 100$ [%]
12. The volume productivity is calculated $= x_{hi} - x_{lo}$
13. The solids volume fraction at isolation is calculated $= (x_{hi} - x_{lo}) / (\text{solids density (mg/ml)})$
14. The productivity, yield and maximum allowable solids fraction at isolation are defined.
15. The Excel logical “AND” and “IF” functions are used to automatically highlight the solvents that meet these targets.

In this example a productivity of 100 kg/m³, yield of >85% and Maximum solids fraction at isolation of 0.3 are specified. The solvents that match these constraints are 1,4-dioxane, Ethanol, Isobutanol, Pentanol, Propanol, Isopropyl alcohol, 1,1,1-Trichloroethane and Water. On the basis of these results the first choice of a cooling crystallization from a single solvent appears feasible and an antisolvent addition should not be required. From this list the alcohols and water are certainly the best choices from a health, safety and environmental

perspective. Water should probably be excluded because Cimetidine is known to form hydrates.

To design an effective crystallization process to generate the commercially available Form A, we must now look at the relative stability of the known polymorphic forms. As discussed previously in section 6.0:

- Form C has an enantiotropic relationship with Forms A and B.
- Forms A and B have a monotropic relationship, with Form B the most thermodynamically stable at all temperatures.

A plot of the ideal solubility curves can be used to identify the transition temperatures for the enantiotropic relationships. Form C is the most stable polymorph at high temperature, with a transition to Form B at 20 °C. The Form C to A transition occurs at 11 °C.

It is clear that kinetic effects must be utilized in the design of a process to make the commercially available Form A, because it is never the most thermodynamically stable form. Information from the literature and patents in reference [14] indicates that Form A can be successfully isolated from Acetonitrile, Acetone, Methyl isobutyl ketone, Toluene, the C2 to C4 alkenols, Ethanol, Methanol and Propan-2-ol. In these solvents it is likely that solvation is favourable to the nucleation rate of Form A or detrimental to crystal growth of the other forms, or both. For a new development compound there should be similar solvent interaction data available from polymorph screening experiments.

For the purpose of this case study we will select Isopropyl alcohol as the crystallization solvent and assume that the NRTL-SAC solubility curve for Form A has been confirmed as reasonably accurate in the laboratory. If experimental solubility data is measured in IPA then it can be fitted to a more accurate (but non predictive) thermodynamic model such as NRTL or UNIQUAC at this point, taking care with analysis of the solid phase in equilibrium. As the activity coefficient model only relates to species in the liquid phase we can use the same model with each different set of ΔH_m and T_m data to calculate the solubility of the other polymorphs of Cimetidine, as shown in Figure 21. True polymorphs only differ from each other in the solid phase and are otherwise chemically identical.

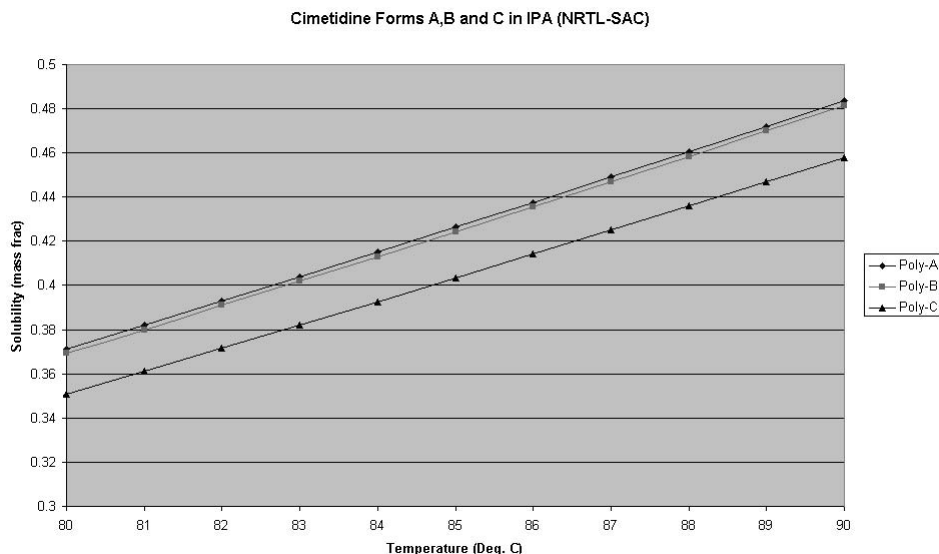


Figure 21: Predicted Solubility of Cimetidine Polymorphs A,B,C in 2-Propanol by NRTL-SAC

In Figure 21. the temperature difference between the polymorphs at a value of 0.46 mass fractions is approximately 2 Deg C. This is much smaller than the metastable zone width for most pharmaceuticals and it is therefore quite probable that a saturated solution can be cooled from 90 °C to 87 °C without precipitation of Form C. Once saturated with respect to Form A we can then seed with crystals of Form A which should then grow preferentially and minimise the chance that Forms B or C will nucleate. A Lasentech FBRM probe could be used in the laboratory at this point to track the rate of growth against different cooling profiles to help match the rate at which supersaturation is being created to the rate of crystal growth. Using an on-line method for the solution phase concentration, such as UV-Vis or FT-IR would gather further information on the growth rate and degree of supersaturation. The temperature should be reduced as quickly as the seed growth rate allows, to minimise the chance of solution mediated polymorphic transformation. Once cooled the system should be isolated by filtration or centrifugation and then washed to remove residual impurities, followed by vacuum or hot nitrogen drying. Given that the relative transition temperatures may be exceeded during drying and storage there is still a potential risk of solid phase transformation which should be assessed by stability trials.

Table 10: Cimetidine Solubility Data for Single Solvents in mg/ml of solution at 25°C [14].

Solvent	CAS No.	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Mean	Standard Deviation	% SD
Octane	111-65-9	8.7E-5	8.37E-5	1.76E-5	1.2E-4			1.17E-4	4.28E-5	36.7
Diethyl ether	60-29-7	2.02E-3	8.76E-4	1.9E-3	2.91E-3	1.01E-3		1.74E-3	8.3E-4	47.6
Ethyl ethanoate	141-78-6	0.428	0.372	0.413	0.417	0.412	0.382	0.404	0.022	5.4
Butan-2-one	78-93-3	3.034	2.781	3.167	2.954	2.842	2.982	2.960	0.138	4.65
Acetone	67-64-1	4.206	3.884	3.901	3.713	3.62	3.767	3.849	0.204	5.3
Dichloromethane	75-09-2	0.417	0.407	0.495	0.439	0.43	0.389	0.430	0.037	8.5
Propan-2-ol	67-63-0	12.27	12.32	12.84	12.38	12.04		12.370	0.293	2.4
Acetonitrile	75-05-8	2.6	2.71	2.47	2.58	3.01	2.67	2.673	0.184	6.9
Ethanol	64-17-5	38.34	36.98	36.12	37.58			37.26	0.94	2.5
Methanol	67-56-1	133.28	161.16	144.01	135.37			143.46	12.68	8.8
Propane-1,2-diol	57-55-6	94.66	94.05	89.57	89.75	86.37	80.85	89.21	5.13	5.8
Ethane diol	107-21-1	130.49	131.6	133.34	128.75	127.36		130.31	2.37	1.8
Glycerol	56-81-5	29.58	32.12	30.53	34.34			31.64	2.08	6.6
Water	7732-18-5	5.91	6.14	6.26	6.01	6.44	5.70	6.08	0.26	4.3

Table 11: Cimetidine Solubility Data for Binary Solvents in mg/ml of solution at 25°C [14]

Binary Solvent (v / v)	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Mean	Standard Deviation	% SD
50% ethane diol / ethanol	182.08	174.8	165.49	161.04	156.25		167.932	10.455	6.23
75% ethane diol / water	78.96	76.28	79.16	80.45	79.65		78.9	1.573	2.0
50% ethanol / methanol	73.8	72.76	77.8	75.11	84.84	76.47	76.8	4.33	5.6
80% ethanol / water	137.1	127.1	129.4	121.2	114.7		125.9	8.47	6.7
75% ethanol / water	106.98	143.19	124.67	129.09	129.92		126.77	13.05	10.3
60% ethanol / water	124.08	115.88	127.04	113.95	115.88		119.366	5.8	4.9
40% ethanol / water	59.65	54.74	53.42	54.06	54.95		55.36	2.47	4.5
25% ethanol / water	18.27	17.9	18.16	18.27	17.53	17.79	17.987	0.298	1.66
10% ethanol / water	10.479	9.543	9.858	9.639	9.877		6.077	0.262	4.31

2.8 Conclusions

The design of crystallization processes for the manufacture of Active Pharmaceutical Ingredients is a significant technical challenge to Process Research and Development groups throughout the Pharmaceutical and related industries. It requires an understanding of both the thermodynamic and kinetic aspects of crystallization, to ensure that the physical properties of the product will consistently meet specification. Failure to address these issues may lead to production problems associated with crystal size, shape and solubility, and to dissolution and bioavailability effects in the formulated product.

With current levels of scientific knowledge about solubility, polymorphism and crystallization kinetics it is necessary to apply a combination of experiment and theory to the process of solvent selection and crystallization process design. There are potential efficiency gains to be realized in this area, through the application and development of computer aided design methods, some of which have been demonstrated in the Cimetidine case study. As the world's pharmaceutical marketplace drives companies to achieve higher levels of efficiency in process design these software tools will become more important. The complexities associated with crystallization science, pharmaceutical systems and scale-up effects, means that it is unlikely that theoretical methods will replace experiment in the near future. Efficient design and competitive advantage will continue to require the correct balance between theory and experimental practice.

Ab initio methods for polymorph, hydrate and solvate prediction are highly prized by the industry and good progress has been made in this field in recent years. This work is still a number of years from routine commercial application however, and polymorph screening experiments together with crystal structure determination, remain critical tasks for today's Pharmaceutical companies.

Solubility modelling with activity coefficient methods is an under-utilized tool in the pharmaceutical sector. Within the last few years there have been several new developments that have increased the capabilities of these techniques. The NRTL-SAC model is a flexible new addition to the predictive armory and new software that facilitates local fitting of UNIFAC groups for Pharmaceutical molecules offers an interesting alternative. Quantum chemistry approaches like COSMO-RS [25] and COSMO-SAC [26] may allow realistic *ab-initio* calculations to be performed, although computational requirements are still restrictive in many corporate environments. Solubility modelling has an important role to play in the efficient development and fundamental understanding of pharmaceutical crystallization processes. The application of these methods to industrially relevant problems, and the development of new

databases that are specific to pharmaceutical type molecules will add to their importance over the coming years.

Predictive methods are most valuable to the solvent selection process, particularly in systems that require mixed solvents, where the number of permutations is high. New, affordable and high throughput solubility screening equipment is gaining popularity within the industry, however most of these devices do not yet include solid state analysis. The large quantities of data that can be generated by these methods will benefit from thermodynamic modelling to help identify outliers, where new polymorphs may have appeared or where chemical reaction and degradation have occurred. These improvements in measurement techniques should in turn yield improvements in the accuracy and applicability of the thermodynamic models. There is an important role to be played in these developments by industry because much of the measured data on pharmaceutical systems is not published, even though it is of significant value to model developers. An increase in scientific publications or collaboration with model developers will yield significant benefits to the industry.

NRTL-SAC has been demonstrated through the case study on Cimetidine as a valuable aid to solubility data assessment and targeted solvent selection for crystallization process design. The average model error is typically $0.5 * \ln(x)$ [1] and is sufficient as a solvent screening tool. Methods that can deliver greater accuracy would increase the value and utility of these techniques. It is impressive in the case of Cimetidine that the NRTL-SAC correlation is capable of reasonable accuracy and predictive capability on the basis of just 2 fitted parameters. Further work to extend the solvent database and optimize the descriptive parameters will be beneficial, and are planned by the developers.

It is estimated that half of all pharmaceuticals are formulated as salts, to achieve increased stability and bioavailability [13]. Predictive solubility methods are very limited for this area, and the development of new models to address this category is very important. The NRTL-SAC model has recently been extended by C.-C. Chen. and Y. Song to represent such electrolytic solutes, that partly dissociate to ions in solution. This extension has been achieved by the addition of one new segment type into the preceding NRTL-SAC model. NRTL-SAC thus becomes a limiting case of the eNRTL-SAC formulation [27].

The most important area in the pharmaceutical and related industries for the application of thermodynamic models is in solid-liquid equilibria. Once developed these same models are applicable to a range of unit operations. Aqueous solubility and concerns about pharmaceuticals in the environment is an obvious extension. Liquid-Liquid extraction and distillation are frequently used operations, and techniques that predict the partitioning and impact of

dissolved solutes are often desired, although rarely available at the necessary levels of accuracy. The impact of solubility on drying performance is also important and frequently defines the cycle time for a production process. Similar techniques could be applied to chromatography, which is an important purification technique in the early stages of process development and particularly relevant to chiral compounds. Solvent selection for chemical reaction is the most difficult area that can benefit from predictive thermodynamic models. Many of these unit operations are combined together in each manufacturing step, and the holistic task of solvent selection is typically constrained by many simultaneous requirements. A rigorous thermodynamic framework which is capable of predicting the behaviour across all of these unit operations will facilitate the use of optimization algorithms for solvent selection and process design. Such techniques are already available though software like ProCAMD. Further developments in the accuracy of thermodynamic models to pharmaceutical systems, and the flexibility of the software design tools offers the potential for significant advances in process design efficiency and environmental performance.

The requirement to model and predict physical properties and physicochemical interactions between an API solute and solvents is not only important during manufacture. It is also important during formulation design and delivery of the drug to its site of action in the human body. Pharmacokinetics is the science of predicting and modelling the uptake, distribution, breakdown and excretion of drug substances. Solubility in body fluids and tissues, at different pH levels are of critical importance. Parameters such as LogD and LogP are often used to screen new drug molecules and there is a potential application of activity coefficient models in this area. Whilst physicochemical properties of the drug are important to its behaviour in the body it should be recognized that active transport across membranes, biotransformation and metabolism can play a more significant role in many drug interactions.

Clinical research groups are responsible for the discovery of new chemical entities, to target and interrupt disease pathways. It is common for drug products to come from families where the active backbone that targets the desired receptor is the same, and different side chains are added to achieve activity in the body. The development of thermodynamic methods that facilitate this approach will have an obvious advantage in reducing data requirements for the life science industries.

I hope that this chapter provides a fitting introduction to the complex task of active pharmaceutical ingredient product design through crystallization, and most importantly that it will stimulate work and encourage further growth in the application of thermodynamic models and optimization techniques in this area.

Acknowledgements

I would like to thank C. Westwood of AstraZeneca for permission to use solubility data and polymorph descriptions of Cimetidine from her MPhil thesis, together with her supervisors, G. Steele of AstraZeneca and M. Aulton of De Montfort University. I would also like to thank C.-C. Chen of Aspen Technology for his technical support in applying the NRTL-SAC model, together with Paul Mathias of Fluor Corporation and Thomas Veron of INSA for their preliminary studies on Cimetidine. The contributions of R. Gani through teaching, constructive support and the SoluCALC and ProCAMD analysis are gratefully received. Thanks are extended to Ron Roberts of AstraZeneca for preparing the crystal structure images and to I. McConvey and B. Fox for helpful comments on the manuscript. Thanks also to my wife Claire and family, for their support and encouragement.

References

1. Chen, C.-C., Song, Y., 2004, Solubility Modeling with a Non-Random Two-Liquid Segment Activity Coefficient Model, *Ind. Eng. Chem. Res.*, 43, 8354-8362.
2. Gani, R., 2004, Chemical product design: Challenges and opportunities, *Computers and Chemical Engineering*, 28, 2441-2457.
3. Gani, R., 2004, Computer-aided methods and tools for chemical product design, *Trans IChemE*, 82 1494-1504.
4. ICAS Documentation. 2003, Internal Report PEC03-XX, CAPEC, Department of Chemical Engineering, Technical University of Denmark (www.capec.kt.dtu.dk)
5. Mullin, J.W., 2001, *Crystallisation*, Fourth Edition, Butterworth-Heinemann.
6. Davey, R.J., Garside J., 2000, *From Molecules to Crystallizers – An Introduction to Crystallization*, Oxford University Press.
7. Smith, J.M., Van Ness, H.C., Abbott, M.M., 1996, *Introduction to Chemical Engineering Thermodynamics*, Fifth Edition, McGraw Hill Companies, Inc.
8. Walas, S.M., 1985, *Phase Equilibria in Chemical Engineering*, Butterworth Publishers.
9. Brittain, H.G., et. al., 1999, *Polymorphism in Pharmaceutical Solids*, Marcel Dekker, Inc.
10. Davey, R.J., et. al., 2003, A Whole Output Strategy for Polymorph Screening: Combining Crystal Structure Prediction, Graph Set Analysis, and Targeted Crystallization Experiments in the Case of Diflunisal., *Crystal Growth and Design*, Vol. 3, No. 2, 151-158.
11. Jones, H.P., Davey, R.J., Cox, B.G., 2005, Crystallization of a Salt of a Weak Organic Acid and Base: Solubility Relations, Supersaturation Control and Polymorphic Behaviour, *J. Phys. Chem. B*, 109, 5273-5278.
12. Karunanithi, A.T., Achenie, L.E.K., Gani, R., 2005, A Computer Aided Molecular Design Framework for Crystallization Solvent Design, *Chemical Engineering Science*, In Press.

13. Davey, R.J., Blagden, N., Righini, S., Alison, H., Quayle, M.J., Fuller, S., 2001, Crystal Polymorphism as a Probe for molecular Self-Assembly during Nucleation from Solutions: The Case of 2,6-Dihydroxybenzoic Acid, *Crystal Growth and Design*, Vol. 1, No. 2, 59-65.
14. Westwood, M.C, Aulton, M., Steele, G., 1998, A Study on the Polymorphic Forms of Cimetidine, M.Phil Thesis, DeMontfort University, UK.
15. Grunenberg, A., Henck, J-O., Siesler, H.W., 1996, Theoretical Derivation and practical Application of Energy / Temperature Diagrams as an Instrument in Preformulation Studies of Polymorphic Drug Substances, *International Journal of Pharmaceutics*, 129, 147-158.
16. Stahl, P.H.; Wermuth, C.G. (Eds.), 2002, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Verlag Helvetica Chimica Acta, Zürich, Switzerland.
17. Ouvrard, C., Price, S.L., 2004, Toward Crystal Structure Prediction for Conformationally Flexible Molecules: The Headaches Illustrated by Aspirin, *Crystal Growth and Design*, Vol.4, No. 6, 1119-1127.
18. Neumann, M.A., Tedesco, C., Destri, S., Ferro, D.R., Porzio, W., 2002, Bridging the gap – structure determination of the red polymorph of tetrahexylsexithiophene by Monte Carlo simulated annealing, first principle DFT calculations and Rietveld refinement, *Journal of Applied Crystallography*, 35, 3, 296-303.
19. Chemburkar, S. R., et. al., 2000, Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development, *Organic Process R&D*, 4, 413-417.
20. Parsons, A.R., Black, S.N., Colling, R., 2003, Automated Measurement of Metastable Zones for Pharmaceutical Compounds, *Trans IChemE*, 81, 700-704.
21. Birch, M., Fussell, S.J., Higginson, P.D., McDowall, N., Marziano, I., 2005, Towards a PAT-Based Strategy for Crystallization Development, *Organic Process Research and Development*, 9, 360-364.
22. Achenie, L.E. K., Gani, R., Venkatasubramanian, V., 2003, *Computer Aided Molecular Design: Theory and Practice*. Elsevier, Amsterdam
23. Gani, 2002, ProCAMD Manual, PEC03-25, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).
24. Jacques, J., Collet, A. and Wilen, S.H., 1981, *Enantiomers, Racemates and Resolutions*, Wiley, New York.
25. Schroer, J.W., Ng, K.M., 2001, Simplify Multicomponent Crystallisation, *Chemical Engineering*, 46-53.
26. Chen, C.-C., 1993, A Segment Based Local Composition Model for the Gibbs Energy of Polymer solutions. *Fluid Phase Equilibria*, 83, 301.
27. Renon, H., Prausnitz, J.M., 1968, Local Compositions in Thermodynamic Excess Functions for Liquid Mixtures, *AIChE Journal*, 14, 135.
28. ICH Steering Committee, 1997, ICH Harmonised Tripartite guideline, Impurities: Guideline for Residual Solvents, Q3C. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
29. Fredenslund, A., Jones, R.L., Prausnitz, J.M., 1975, Group Contribution Estimation of Activity Coefficients in Nonideal Liquid Mixtures. *AIChE Journal*, 21, 1086.

30. Kolar, P., Shen, J-W., Tsuboi, A., Ishikawa, T., 2002, Solvent Selection for Pharmaceuticals, *Fluid Phase Equilibria*, 194-197, 771-782.
31. Marrero, J. and Gani, R., ProPred Manual, PEC02-15, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).
32. Klamt, A., Eckert, F., 2000, COSMO-RS: a Novel and Efficient method for the a Priori Prediction of Thermophysical Data of Liquids. *Fluid Phase Equilibria.*, 172, 43.
33. Lin, S.-T., Sandler, S. I., 2002, A Priori Phase Equilibrium Prediction from a Segment Contribution Solvation Model. *Ind. Eng. Chem. Res.*, 41, 899-913.
34. Chen, C.-C., Song, Y., 2005, Extension of NonRandom Two Liquid Segment Activity Coefficient Model for Electrolytes, *Ind. Eng. Chem. Res.*, In Print – expected Oct / Nov.

Nomenclature

Table 12 : Nomenclature and Units

Symbol	Units	Description
A, B, C, D		Constants in Aspen's Ksp equation eq.
x	(mol fraction)	Concentration in the liquid phase.
T	(K)	Temperature
T_m	(K)	Normal melting temperature
ΔH_m	(J.mol ⁻¹)	Specific Enthalpy of melting at T_m
G	(J.mol ⁻¹)	Specific Gibbs free energy
H	(J.mol ⁻¹)	Specific Enthalpy
S	(J.mol ⁻¹ .K ⁻¹)	Specific Entropy
α	(-)	Non-randomness factor in the NRTL-SAC model
γ	(-)	Activity coefficient
τ	(-)	Binary interaction parameter in the NRTL-SAC model

Superscripts:

c_{sat} saturated (equilibrium) concentration of a solid dissolved in a solute

Subscripts:

I, II....	Solid phase polymorph I, II etc.
1,2....	Component 1,2 etc.

Appendix 1 – NRTL-SAC Molecular Parameters For Common Solvents

Table 13: NRTL-SAC molecular parameters for common solvents

Component	X-R	Y-R	Y+R	Z-R
ACETICAC	0.04469	0.16358	0.15715	0.21739
ACETONE	0.13139	0.10865	0.51284	
ACETONIT	0.01773	0.13073	0.88340	
ANISOLE	0.72237			
BENZENE	0.60675		0.18982	
1-BUTANO	0.41448	0.00694		0.48513
2-BUTANO	0.33484	0.08226		0.35457
BUTYLACE	0.31656	0.02977	0.33031	
T-B-M-ET	1.04018	0.21935	0.17189	
CARBONTE	0.71794		0.14065	
CHLOROBE	0.70997		0.42394	
CHLOROFO	0.27822		0.03938	
CUMENE	1.20756		0.54052	
CYCLOHEX	0.89238			
1,2-DICH	0.39409		0.69085	
1,1-DICH	0.52925		0.20841	
1,2DICHL	0.18776		0.83241	
DICHLORO	0.32144		1.26151	
12DIMETA	0.08096	0.19416	0.85821	
DMA	0.06736	0.02984	0.15729	
DMF	0.07253	0.56377	0.37195	
DMSO	0.53210	2.89004		
1,4-DIOX	0.15426	0.08586	0.40146	
ETHANOL	0.25569	0.08105		0.50669
2-ETHOXY	0.07136	0.31825		0.23696
ETHYLACE	0.32246	0.04898	0.42079	
ETHYEGLY		0.14145		0.33781
ETHYLETH	0.37289	0.02486	0.17994	
ETHYLFOR	0.25708		0.28029	
FORMAMID		0.08948	0.34076	0.25245
FORMICAC	0.70662	2.47046		
HEPTANE	1.33965			
HEXANE	1.00000			

ISOBUTYA	1.65989		0.10825	
ISOPROPA	0.55248	0.15385	0.49821	
METHANOL	0.08763	0.14859	0.02742	0.56240
2-METHOE	0.05238	0.04264	0.25132	0.56017
METHYACE	0.23624		0.33701	
3-M-1-B	0.41902		0.53781	0.31417
MBK	0.67305	0.22356	0.46930	
M-CYCLOH	1.16169		0.25054	
MEK	0.24695	0.03579	0.47981	
MIBK	0.67305	0.22356	0.46930	
2-M-1-PR	0.56609		0.06687	0.48494
M-PYRROL	0.19747	0.32160		0.30474
NITROMET	0.02490		1.21620	
PENTANE	0.89763			
1-PENTAN	0.47425	0.22336	0.42618	0.24814
1-PROPAN	0.37459	0.02992		0.51123
2-PROPAN	0.35123	0.06971	0.00318	0.35281
PROPYLAC	0.51363	0.13402	0.58685	
PYRIDINE	0.20476	0.13537	0.17434	
SULFOLAN	0.20968			0.45710
THF	0.23541	0.03977	0.32047	
TETRALIN	0.44289	0.55463		
TOLUENE	0.60352		0.30393	
111TRICE	0.54823		0.28710	
112TRICE	0.42573	0.28483		
XYLENE	0.75833	0.02117	0.31593	
WATER				1.00000
3EAMINE	0.55732	0.10545		
OCTANOL	0.76632	0.03209	0.62449	0.33474

Chapter 3

CAMD Using a Linear GC-Method for the Prediction of Pure Component Properties: Application to Solvent Selection

Leonidas Constantinou^{a*} and Vassilis Vassiliades^b

^a*Frederick Research Center, P.O. Box 24729, Nicosia, Cyprus*

^b*Department of Chemical Engineering, Cambridge University, UK*

3.1 INTRODUCTION

The objective of this chapter is to highlight the application of a CAMD-based methodology for the design and selection of replacement solvents for the paints and ink industry. CAMD means computer aided molecular design where given a set of property targets, the molecules that match the desired property targets, are determined. The target properties of the replacement solvents are estimated by methods based on the Group Contribution (GC) concept. This is an important feature for most CAMD-based methodologies as the same groups are then used to generate and describe the molecular structures. In this chapter, the CAMD-problem for solvent replacement is formulated and solved as a mathematical programming (optimization) problem, where the GC-based property models are considered as constraints. Solvent replacement problems are important for the solvent manufacturer (who would like to introduce new products) as well as solvent users (whose product can be made more competitive by reducing productions costs and improving product quality). Thus, the examples highlighting the application of the CAMD-based methodology serve to serve to illustrate a typical chemical product design problem usually encountered by many chemical product manufacturers.

The two innovative features of this chapter are the following:

- the synergy between property estimation as they are incorporated in the purely predictive GC-based models for estimating properties of organic compounds (such as, Constantinou and Gani, 1994) with the principles of mathematical modeling and optimization in the form of Mixed Integer Linear Programming (MILP), turning the solvent replacement problem of product design into an MILP (optimization) problem;
- the validation of the results through industrial and/or laboratory scale tests, highlighting thereby, aspects of evaluation of the chemical product.

The development of reliable and predictive models for the estimation of properties of organic compounds from only molecular structural information has been the foundation of most CAMD techniques. The GC concept is ideally suited for use within CAMD techniques because it provides a wide application range at very low computational expense and reasonable prediction accuracy. In this chapter, the GC-based property models of Constantinou and Gani (1994) has been employed because they have been found to be one of the most reliable for the estimation of properties of pure organic compounds (Poling et al., 2000). The MILP optimization problem for solvent replacement has been solved through the GAMS software package, and given its mixed integer linear nature, it guarantees the global optimum solution of each problem.

Having established the basic features (property prediction and optimization model) for the CAMD-based methodology, the chapter focuses on three examples of a specific implementation of the methodology - the replacement of solvents that are in the production line of many industrial enterprises. The replacement solvents must exhibit the desired environmental and physicochemical properties and also be environmentally more friendly than the solvent they are replacing.

The three examples related to solvent replacement cover the generation and evaluation of solvent alternatives for Ethyl Glycol Acetate, Ethyl Glycol and Methylene Chloride. Where feasible, the selected solvent alternatives have been tested under conditions of industrial application and/or laboratory scale experiments with very encouraging results.

3.2 PRODUCT DESIGN METHODOLOGY

The designed methodology consists of the following steps as shown in Figure 1.

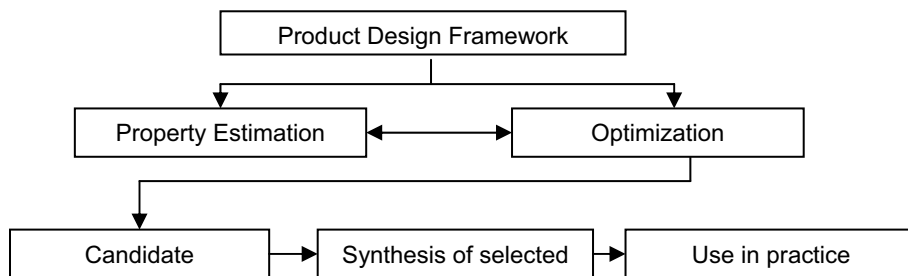


Figure 1: The steps in the Product Design Methodology

3.2.1 Constantinou-Gani Group Contribution Method

According to CAMD-based methodology, the molecular structure of a compound can be described by using two types of groups - simple functional groups (first-order groups), and more complex groups (second-order groups) with first-order groups as building blocks. Each one of these groups has its own contribution to the value of a property, p , regardless of the type of the compound. The first-order groups are the typical set used for mixture properties (Fredenslund et al., 1977). However, the definition of second-order groups has a theoretical basis with a sound physical meaning, and is based on conjugation (Constantinou, 1993). The conjugation principle allows the definition of functional groups with physical meaning. More information about the background of the method is given elsewhere (Constantinou and Gani, 1994).

The GC-based model of Constantinou-Gani can be represented for any property p , as follows,

$$f(p) = \sum_{i=1}^{N1} n_i \cdot F_i + W \sum_{j=1}^{N2} m_j \cdot S_j \quad (1)$$

where, $f(p)$ is a simple function of the property p to be estimated, F_i is the group contribution of the first-order group i which occurs n_i times and S_j is the group contribution of the second-order group j which occurs m_j times. The contribution of the second-order groups is a correction to the first-order approximation. This means that, if W equals to 1, the property is estimated with the contributions of both the first-order and second-order groups. If W equals to 0, then only the first-order approximation is taken into consideration. The

contributions of first and second-order groups can be found in the open literature (Constantinou and Gani, 1994; Constantinou et. al., 1995; Stefanis et al., 2004).

3.2.2 Optimization Technique

The basic GC-model of the Constantinou and Gani method (Eq. 1) as presented above provides the basis for the formulation of the solvent replacement problem as a MILP-optimization problem. For purposes of simplicity, in this chapter, only the first-order approximation is taken into consideration (that is, W is equal to zero). In this way, the functions of the target properties of the generated molecules (solvent replacements) are written as monotonic functions of the property values, thereby, leading to a linear right hand side of the property constraints (property model equation), as follows,

$$\hat{p}_k = f_k(p_k) = \sum_{i=1}^{NI} n_i \cdot F_{k,i} \quad k = 1, 2, \dots, NP \quad (2)$$

In Eq. 2, index p indicates a specific target property from the NP number of properties considered, p_k is the value of the property k for the given compound and $f_k(p_k)$ is the corresponding monotonic functional transformation of this value.

The Normalized deviation of the transformed property is given by,

$$\frac{f_k(p_k) - f_k(p_k^t)}{f_k(p_k^t)} = \varepsilon_k \quad (3)$$

where, the new variable ε_k is continuous and positive. The objective function is now defined as,

$$\min \sum_{k=1}^{NJ} \varepsilon_k \quad (4)$$

and the resulting mathematical model consisting of Eqs. 2-4 is classified as a Mixed-Integer Linear Programming (MILP) Problem.

In the above MILP-optimization problem, Euler's theorem for the generation of stable and feasible molecular structures (fully connected graphs) needs to be added as a condition in order to ensure the generation of chemically feasible molecules. This condition is mathematically formulated as,

$$\sum_{j=1}^{NTOTAL} A_j^{NSB} n_j = 2(n_t + n_{rings} - 1) \quad (5)$$

$$\sum_{j=1}^{NTOTAL} n_j = n_t \quad (6)$$

where, the summation on the left-hand side of Eq. 5 is the number of free bonds A_j^{NSB} per first-order group j , while n_t and n_{rings} on the right-hand side are the total number of groups and the number of rings, respectively.

3. 3 CASE STUDY

The CAMD-based MILP-optimization problem, as formulated above, has been solved for the replacement of solvents that are currently used in small to medium sized enterprises.

The step by step solution procedure employed to solve the MILP-optimization problem is given below.

1. Determine a set of pure component properties (design targets) of the solvent under replacement (specify the goal values for the properties together with upper and lower bounds)
2. Set any additional conditions of the optimization problem (such as the environmental impact)
3. Solve the optimization problem through an appropriate solver (such as the GAMS software package)
4. Identify potential candidates for further studies from the list obtained from step 3
5. Perform further analysis of the candidate molecules to select between one to two replacements of the solvent under study
6. Test the selected candidates from step 5, if they are available or consider synthesizing them.

The above solution procedure has been applied to find replacement solvents for the following solvents: Ethyl Glycol Acetate, Ethyl Glycol and Methylene Chloride. These three solvents are extensively used in the paints and ink industry, although, recent studies have shown that they carry an appreciable environmental burden in addition to being found harmful for the health of the people exposed to them (for example, employees in the manufacturing plants and/or consumers).

The objective of this case study is to highlight the application of the step by step solution procedure for the three examples of the solvent replacement problem. For the case of replacement of Ethyl Glycol Acetate, the output of the MILP-optimization problem solution obtained through GAMS is given in the Appendix. The corresponding input file can be obtained from the corresponding author or from the co-editor of this volume (R. Gani – rag@kt.dtu.dk).

3.3.1 Replacement of Ethyl Glycol Acetate

For the replacement of this solvent, all the steps mentioned above has been followed:

Step 1: Pre-selected Properties

The pre-selected pure component properties are among those covered by the Constantinou and Gani method (Constantinou and Gani, 1994; Constantinou et al., 1995, Stefanis et al., 2004). In Table 1, these properties are listed together with their experimental values (CAPEC Database, 2002) for Ethyl Glycol Acetate. That is, the values listed in Table 1, represent the design target goals and the upper and lower bounds are set at $\pm 10\%$ of these values. It can be noted that the pre-selected properties consist of four properties that describe the corresponding state behavior (Acentric Factor, Critical Temperature, Critical Pressure and Critical Volume) of a molecule and two that are very closely related to the environmental performance of a chemical (Normal Boiling Point and Total Solubility Parameter).

Step 2: Additional Conditions for the Molecular Design

During the formulation of the optimization problem, two additional characteristics are included,

- (1) Only a maximum of one aromatic ring is allowed to the candidate molecular structures
- (2) Groups with double or triple bonds are excluded

The above conditions limit the search space by removing candidates that are most likely not to satisfy the property constraints.

Table 1: Pre-selected properties for the design of alternatives for Ethylene Glycol Acetate

Property	Value
Acentric Factor	0.5332
Critical Temperature	597 K
Critical Pressure	24.278 Bar
Critical Volume	0.4590 cm ³ /mol
Normal Boiling Point	429.45 K
Total solubility parameter	18.7611

Steps 3 and 4: MILP-optimization Problem Solution

The solution of the MILP-optimization problem gave the candidate solvents shown in Figure 2 (drawn in IUPAC form). The results from GAMS is given in the Appendix. It is important to note that none of these molecular structures are commercially available. Therefore, in order to test them, it is first necessary to synthesize them. Consequently, steps 5-6 have not been performed for these molecules. It is, however, very likely that these molecules will be chemically feasible and stable.

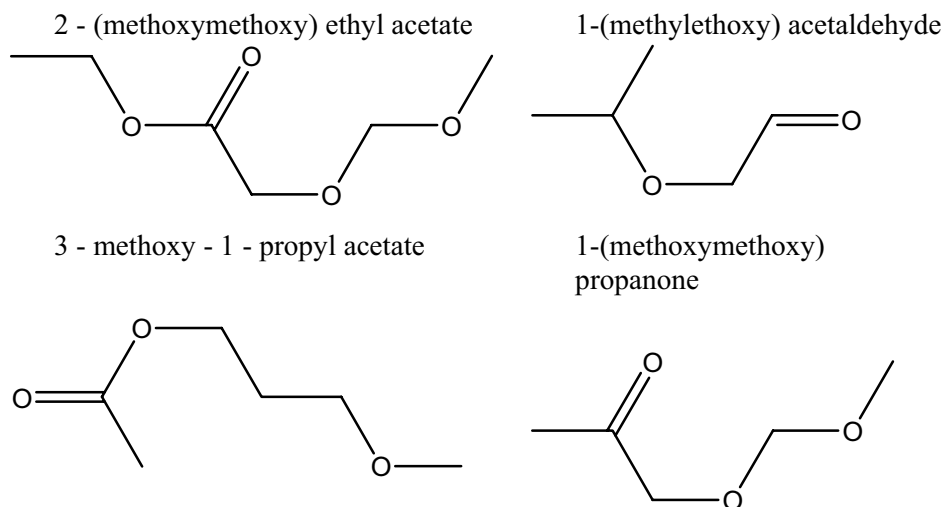


Figure 2: Generated solvent replacements for Ethyl Glycol Acetate

3.3.2 Replacement of Ethyl Glycol

Step 1: Pre-Specified Properties

Table 2 lists the properties that were selected as in previous example, along with their target values corresponding to the properties of Ethyl Glycol, the solvent to be replaced.

Table 2: Pre-Selected Properties for the design of alternatives of Ethyl Glycol

Property	Value
Acentric Factor	0.7591
Critical Temperature	569 K
Critical Pressure	41.846 Bar
Critical Volume	0.2940 cm ³ /mol
Normal Boiling Point	408.15 K
Total solubility parameter	21.5411

Step 2. Additional Conditions

Similar to the previous example, only one aromatic ring is allowed to the candidate molecular structures and groups with double or triple bonds are excluded.

Steps 3 and 4. MILP-optimization Problem Solution

The candidate compounds that were generated by solving the MILP-optimization problem through GAMS are shown in Fig. 3.

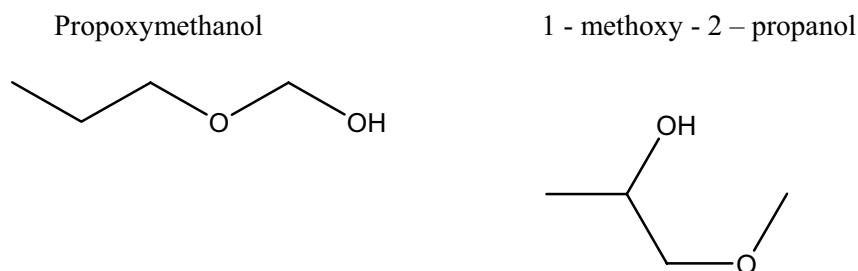


Figure 3: Generated replacement solvents for Ethyl Glycol

Steps 5 and 6: Testing of candidate solvents

The two candidate compounds are commercially available. These candidate solvents were purchased and tested in the laboratories of paint industries (Constantinou 2005). It was found that the solvent 1-methoxy-2-propanol was very successful in replacing Ethyl Glycol. When it was tested in larger amounts (under actual plant operation), it was also found to be equally successful. Consequently, 1-methoxy-2-propanol replaced Ethyl Glycol very successfully, while at the same time making a lower environmental impact. This example highlights the breadth of the CAMD-based methodology in terms of its ability to provide realistic solutions which are theoretically consistent and practically applicable.

3.3.3 Replacement of Methylene Chloride

Step 1: Pre-specified Properties

Similar to the previous examples, the pre-selected target properties for the replacement of methylene chloride as a solvent, are listed in Table 3.

Table 3: Pre-selected properties for the design of alternatives for Methylene Chloride

Property	Value
Acentric Factor	0.1986
Critical Temperature	510 K
Critical Pressure	61 Bar
Critical Volume	0.1850 (m ³ /kmol)
Normal Boiling Point	312.79 K
Total solubility parameter	18.70

Step 2: Additional Conditions

The same conditions as in cases 1 and 2 were applied.

Step 3 and 4: MILP-optimization Problem Solution

The results from the solution of the MILP-optimization problem obtained through GAMS gave the candidates shown in Fig. 4.

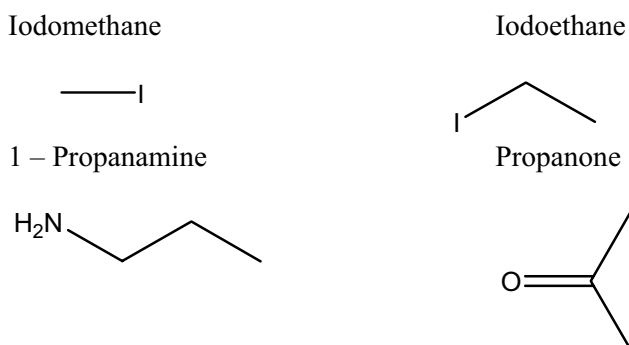


Figure 4: Solvent replacements for Methylene Chloride

Steps 5 and 6: Testing of Candidate Solvents

In Fig.4, two of the replacement solvents are Iodomethane and Iodoethane. As very little information can be found about these molecules and since sufficient information with respect to their effect on human health is not known, they are not considered for further evaluation. Moreover, these molecules are known to easily decompose.

Among the remaining two solvent replacement candidates, Propylamine can be corrosive for metals like Aluminium and Copper and it is extremely flammable. For these reasons, this candidate is also rejected.

The remaining solvent candidate, i.e., Propanone was tested as a replacement of Methylene Chloride under laboratory conditions and the results were found to be promising (Constantinou 2005). Eventhough it was not applied under actual industrial conditions, Propanone appears to be a likely replacement for Methylene Chloride.

3.4 CONCLUSIONS

A simple application in chemical product design employing a CAMD-based methodology for replacement of solvents has been presented and its application highlighted through three examples. Successful application of the CAMD technique requires simple and yet consistent, correct and flexible methods for property estimation. The GC-based property estimation models provide these features as well as thermodynamic insights needed to formulate the specific chemical product design (in this case, molecular design) problems. Also, it has been shown that the solvent replacement problem can be formulated and solved as a MILP-optimization problem. For the three examples of application, it was possible to find feasible replacements. For two cases (Ethyl Glycol and Methylene Chloride), the replacement solvents were tested and found to be satisfy the predicted behaviour. Specifically, as a replacement of Ethyl Glycol Acetate, the solution of the MILP-optimization problem generated new stable molecular structures, which an interested chemical producer may decide to synthesize and test. As a replacement for Methylene Chloride, Propanone has been found to satisfy the tests that were carried out under laboratory conditions. Last, but not least, as an alternative to Ethyl Glycol, 1- Methoxy-2-Propanol was found and tested under laboratory conditions and under actual industrial operations. The solvent was found to give very satisfactory performances.

REFERENCES

- Constantinou, L., and R. Gani., "New Group Contribution Method for estimating properties of Organic Compounds", *AIChE J.*, 40/10, 1697, (1994).
- Constantinou, L., R. Gani, and J. P. O'Connell, "Estimation of the acentric factor and the liquid molar volume at 298K through a new group contribution method". *Fluid Phase Equilibria* 103, 11, (1995).
- Constantinou, L., "Estimation of Properties of Acyclic Organic Compounds through Conjugation", *Ph. D. Dissertation*, Department of Chemical Engineering and Institute for Systems Research, University of Maryland, College Park, USA, also ISR 93-4, (1993).
- Constantinou, L., "An Innovative Methodology for Molecular Design", Final Report of the 10/5th/2002 Project, (2005)
- Fredenslund, Aa., J. Gmehling, and P. Rasmussen, "*Vapor Liquid Equilibria using INIFAC*" Elsevier Scientific, Amsterdam (1977).
- Poling, B.E., J.M. Prausnitz and J.P. O'Connell, "*The Properties of Gases and Liquids*", McGraw-Hill, 5th Edit., (2000)
- Stefanis, E., L. Constantinou, and C. Panayiotou, "Accurate Group-Contribution Method for Predicting Pure Component Properties of Biochemical and Safety Interest", *Industrial and Engineering Chemistry Research*, **43**, 6253-6262, (2004)

Appendix B. GAMS output for the case of Ethyl Glycol Acetate

Page 1
General Algebraic Modeling System
Compilation

COMPILATION TIME = 0.070 SECONDS 0.8 Mb WIN207-133

Page 2
General Algebraic Modeling System
Model Statistics SOLVE group1norminf Using MIP From line 483

MODEL STATISTICS

BLOCKS OF EQUATIONS 16 SINGLE EQUATIONS 134
BLOCKS OF VARIABLES 18 SINGLE VARIABLES 661
NON ZERO ELEMENTS 1316 DISCRETE VARIABLES 541

GENERATION TIME = 0.120 SECONDS 1.6 Mb WIN207-133
EXECUTION TIME = 0.120 SECONDS 1.6 Mb WIN207-133

Page 3
General Algebraic Modeling System
Solution Report SOLVE group1norminf Using MIP From line 483

S O L V E S U M M A R Y

MODEL group1norminf OBJECTIVE obj
TYPE MIP DIRECTION MINIMIZE
SOLVER CPLEX FROM LINE 483

**** SOLVER STATUS 1 NORMAL COMPLETION
**** MODEL STATUS 1 OPTIMAL
**** OBJECTIVE VALUE 0.1316

RESOURCE USAGE, LIMIT 0.931 1000.000
ITERATION COUNT, LIMIT 633 1000000

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

MIP Solution: 0.131573 (633 iterations, 248 nodes)
Final LP: 0.131573 (0 iterations)

Best integer solution possible: 0.131573
Absolute gap: 0.000000
Relative gap: 0.000000


```

**** REPORT SUMMARY :      0      NONOPT
                           0 INFEASIBLE
                           0 UNBOUNDED

```

Page 4

General Algebraic Modeling System
Execution

```

----      489
=====
----      490 Problem solution with INFINITY NORM OBJECTIVE
----      491
=====
493 VARIABLE obj.L          = 0.13157321 the objective function
494 VARIABLE epsilonall.L   = 0.13157321
495 VARIABLE nlq.L = 5.00000000 the total number of first order groups

----      495 VARIABLE n1.L the number of first order groups

1 1.00000000,      7 1.00000000,      24 1.00000000,      33 2.00000000

496 VARIABLE nrings.L = 0.00000000 the total number of rings introduced

----      496 VARIABLE naromatic.L          = 0.00000000
----      496 VARIABLE yaromatic.L          = 0.00000000

----      497 PARAMETER ft the target value for a property

tcli 27.00471986,  pcli 0.10871498,  vcli 0.46335000
tbli 8.17801062,  wli 1.98861294,  solpar 5.385114E+2

----      497 VARIABLE f.L the properties computed for the mix of groups

tcli 30.04470000,  pcli 0.09441100,  vcli 0.50629000
tbli 9.18410000,  wli 1.81451000,  solpar 5.633300E+2

499 VARIABLE elhs.L          = 8.00000000 the lhs of the edges equation

----      499 VARIABLE erhs.L = 8.00000000 the rhs of the edges equation

```

Page 5

General Algebraic Modeling System
Model Statistics SOLVE group1norminfcut1 Using MIP From line 532

MODEL STATISTICS

BLOCKS OF EQUATIONS	17	SINGLE EQUATIONS	135
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	661
NON ZERO ELEMENTS	1836	DISCRETE VARIABLES	541
GENERATION TIME	=	0.060 SECONDS	1.6 Mb WIN207-133
EXECUTION TIME	=	0.060 SECONDS	1.6 Mb WIN207-133

Page 6

General Algebraic Modeling System
 Solution Report SOLVE group1norminfcut1 Using MIP From line 532

S O L V E S U M M A R Y

MODEL	group1norminfcut1	OBJECTIVE	obj
TYPE	MIP	DIRECTION	MINIMIZE
SOLVER	CPLEX	FROM LINE	532

**** SOLVER STATUS 1 NORMAL COMPLETION

**** MODEL STATUS 1 OPTIMAL

**** OBJECTIVE VALUE 0.1464

RESOURCE USAGE, LIMIT	0.200	1000.000
ITERATION COUNT, LIMIT	757	1000000

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
 Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

MIP Solution: 0.146429 (757 iterations, 423 nodes)
 Final LP: 0.146429 (0 iterations)

Best integer solution possible: 0.146429

Absolute gap: 0.000000

Relative gap: 0.000000

**** REPORT SUMMARY : 0 NONOPT
 0 INFEASIBLE
 0 UNBOUNDED

Page 7

General Algebraic Modeling System
 Execution

```

---- 537
=====
---- 538 Problem solution with INFINITY NORM OBJECTIVE AND ONE CUT
---- 539
=====
541 VARIABLE obj.L = 0.14642857 the objective function
542 VARIABLE epsilonall.L = 0.14642857
543 VARIABLE nlg.L = 7.000000000 the total number of first order groups

---- 543 VARIABLE n1.L the number of first order groups

1 3.00000000, 3 2.00000000, 6 1.00000000, 30 1.00000000

544 VARIABLE nrings.L = 0.000000000 the total number of rings introduced

---- 544 VARIABLE naromatic.L = 0.000000000
---- 544 VARIABLE yaromatic.L = 0.000000000

---- 545 PARAMETER ft the target value for a property

tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2

---- 545 VARIABLE f.L the properties computed for the mix of groups

```

```

tcli  30.32380000,  pcli  0.09279600,  vcli  0.50511000
tbli  8.85570000,  wli  1.95254000,  solpar 5.974600E+2

547 VARIABLE elhs.L      = 12.00000000 the lhs of the edges equation
---- 547 VARIABLE erhs.L = 12.00000000 the rhs of the edges equation

```

Page 8

General Algebraic Modeling System
 Model Statistics SOLVE grouplnorminfcut2 Using MIP From line 581

MODEL STATISTICS

BLOCKS OF EQUATIONS	18	SINGLE EQUATIONS	136
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	661
NON ZERO ELEMENTS	2356	DISCRETE VARIABLES	541
GENERATION TIME	=	0.060 SECONDS	1.6 Mb WIN207-133
EXECUTION TIME	=	0.070 SECONDS	1.6 Mb WIN207-133

Page 9

General Algebraic Modeling System
 Solution Report SOLVE grouplnorminfcut2 Using MIP From line 581

S O L V E S U M M A R Y

MODEL	grouplnorminfcut2	OBJECTIVE	obj
TYPE	MIP	DIRECTION	MINIMIZE
SOLVER	Cplex	FROM LINE	581

```

**** SOLVER STATUS      1 NORMAL COMPLETION
**** MODEL STATUS       1 OPTIMAL
**** OBJECTIVE VALUE          0.1567

```

RESOURCE USAGE, LIMIT	0.220	1000.000
ITERATION COUNT, LIMIT	851	1000000

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
 Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

```

MIP Solution:          0.156687 (851 iterations, 477 nodes)
Final LP:              0.156687 (0 iterations)

```

```

Best integer solution possible:          0.156687
Absolute gap:              0.000000
Relative gap:              0.000000

```

```

**** REPORT SUMMARY :      0      NONOPT
                          0      INFESIBLE
                          0      UNBOUNDED

```

Page 10

General Algebraic Modeling System
 Execution

```

---- 586
=====
---- 587 Problem solution with INFINITY NORM OBJECTIVE AND TWO CUTS
---- 588

```

```
=====
590 VARIABLE obj.L           = 0.15668669 the objective function
591 VARIABLE epsilon11.L     = 0.15668669
592 VARIABLE nl1.L = 6.00000000 the total number of first order groups
---- 592 VARIABLE n1.L the number of first order groups
1 3.00000000, 7 1.00000000, 19 1.00000000, 26 1.00000000
593 VARIABLE nrings.L = 0.00000000 the total number of rings introduced
---- 593 VARIABLE naromatic.L = 0.00000000
---- 593 VARIABLE yaromatic.L = 0.00000000
---- 594 PARAMETER ft the target value for a property
tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2
---- 594 VARIABLE f.L the properties computed for the mix of groups
tcli 31.23600000, pcli 0.10972900, vcli 0.48755000
tbli 9.43230000, wli 1.96187000, solpar 5.973800E+2
596 VARIABLE elhs.L = 10.00000000 the lhs of the edges equation
---- 596 VARIABLE erhs.L = 10.00000000 the rhs of the edges equation
```

Page 11

General Algebraic Modeling System
Model Statistics SOLVE group1norm1 Using MIP From line 606

MODEL STATISTICS

BLOCKS OF EQUATIONS	16	SINGLE EQUATIONS	134
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	1321	DISCRETE VARIABLES	541
GENERATION TIME	=	0.070 SECONDS	1.6 Mb WIN207-133
EXECUTION TIME	=	0.070 SECONDS	1.6 Mb WIN207-133

Page 12

General Algebraic Modeling System
Solution Report SOLVE group1norm1 Using MIP From line 606

S O L V E S U M M A R Y

MODEL	group1norm1	OBJECTIVE	obj
TYPE	MIP	DIRECTION	MINIMIZE
SOLVER	Cplex	FROM LINE	606

```
**** SOLVER STATUS      1 NORMAL COMPLETION
**** MODEL STATUS      1 OPTIMAL
**** OBJECTIVE VALUE          0.4163
```

RESOURCE USAGE, LIMIT	0.230	1000.000
ITERATION COUNT, LIMIT	1185	1000000

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

MIP Solution: 0.416324 (1185 iterations, 424 nodes)
 Final LP: 0.416324 (0 iterations)

Best integer solution possible: 0.416324
 Absolute gap: 0.000000
 Relative gap: 0.000000

**** REPORT SUMMARY : 0 NONOPT
 0 INFEASIBLE
 0 UNBOUNDED

Page 13
 General Algebraic Modeling System
 Execution

```

---- 612
=====
---- 613 Problem solution with NORM-1 OBJECTIVE
---- 614
=====
616 VARIABLE obj.L = 0.41632425 the objective function

---- 617 VARIABLE epsilon.L the property slack variable

tcli 0.01811979, pcli 0.15689630, vcli 0.03591238
tbli 0.00480687, wli 0.00788844, solpar 0.19270046

618 VARIABLE nlg.L = 7.00000000 the total number of first order groups

---- 618 VARIABLE n1.L the number of first order groups

1 4.00000000, 4 1.00000000, 26 1.00000000, 30 1.00000000

619 VARIABLE nrings.L = 0.00000000 the total number of rings introduced

---- 619 VARIABLE naromatic.L = 0.00000000
---- 619 VARIABLE yaromatic.L = 0.00000000

---- 620 PARAMETER ft the target value for a property

tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2

---- 620 VARIABLE f.L the properties computed for the mix of groups

tcli 26.51540000, pcli 0.09165800, vcli 0.47999000
tbli 8.13870000, wli 2.00430000, solpar 4.347400E+2

622 VARIABLE elhs.L = 12.00000000 the lhs of the edges equation

---- 622 VARIABLE erhs.L = 12.00000000 the rhs of the edges equation

```

Page 14
 General Algebraic Modeling System
 Model Statistics SOLVE group1norm1cut1 Using MIP From line 658

MODEL STATISTICS

BLOCKS OF EQUATIONS	17	SINGLE EQUATIONS	135
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	1841	DISCRETE VARIABLES	541

```

GENERATION TIME      =          0.060 SECONDS    1.6 Mb    WIN207-133
EXECUTION TIME       =          0.070 SECONDS    1.6 Mb    WIN207-133

```

Page 15
 General Algebraic Modeling System
 Solution Report SOLVE group1norm1cut1 Using MIP From line 658

S O L V E S U M M A R Y

MODEL	group1norm1cut1	OBJECTIVE	obj
TYPE	MIP	DIRECTION	MINIMIZE
SOLVER	CPLEX	FROM LINE	658

```

**** SOLVER STATUS      1 NORMAL COMPLETION
**** MODEL STATUS      1 OPTIMAL
**** OBJECTIVE VALUE          0.4400

```

```

RESOURCE USAGE, LIMIT      0.360      1000.000
ITERATION COUNT, LIMIT    1999      1000000

```

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
 Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

```

MIP Solution:          0.440011      (1999 iterations, 811 nodes)
Final LP:              0.440011      (0 iterations)

```

```

Best integer solution possible:          0.440011
Absolute gap:          0.000000
Relative gap:          0.000000

```

```

**** REPORT SUMMARY :      0      NONOPT
                          0 INFEASIBLE
                          0 UNBOUNDED

```

Page 16
 General Algebraic Modeling System
 Execution

```

----      664
=====
----      665 Problem solution with NORM-1 OBJECTIVE AND ONE CUT
----      666
=====
668 VARIABLE obj.L          =    0.44001125  the objective function

----      669 VARIABLE epsilonp.L  the property slack variable

tcli  0.05410092,    pcli  0.16124713,    vcli  0.07553685
tbli  0.02617866,    wli   0.06016609,    solpar 0.06278160

670 VARIABLE n1g.L =    5.00000000  the total number of first order groups

----      670 VARIABLE n1.L  the number of first order groups

1  1.00000000,    5  1.00000000,    7  1.00000000,    20 1.00000000
26 1.00000000

```

```

671 VARIABLE nrings.L = 0.00000000 the total number of rings introduced
----
671 VARIABLE naromatic.L = 0.00000000
671 VARIABLE yaromatic.L = 0.00000000
----
672 PARAMETER ft the target value for a property
tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2
----
672 VARIABLE f.L the properties computed for the mix of groups
tcli 28.46570000, pcli 0.09118500, vcli 0.42835000
tbli 8.39210000, wli 2.10826000, solpar 5.723200E+2
674 VARIABLE elhs.L = 8.00000000 the lhs of the edges equation
----
674 VARIABLE erhs.L = 8.00000000 the rhs of the edges equation

```

Page 17

General Algebraic Modeling System
Model Statistics SOLVE grouplnormlcut2 Using MIP From line 709

MODEL STATISTICS

BLOCKS OF EQUATIONS	18	SINGLE EQUATIONS	136
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	2361	DISCRETE VARIABLES	541
GENERATION TIME	=	0.060 SECONDS	1.6 Mb WIN207-133
EXECUTION TIME	=	0.060 SECONDS	1.6 Mb WIN207-133

Page 18

General Algebraic Modeling System
Solution Report SOLVE grouplnormlcut2 Using MIP From line 709

S O L V E S U M M A R Y

MODEL	grouplnormlcut2	OBJECTIVE	obj
TYPE	MIP	DIRECTION	MINIMIZE
SOLVER	Cplex	FROM LINE	709
**** SOLVER STATUS	1 NORMAL COMPLETION		
**** MODEL STATUS	1 OPTIMAL		
**** OBJECTIVE VALUE	0.4513		

RESOURCE USAGE, LIMIT	0.340	1000.000
ITERATION COUNT, LIMIT	1752	1000000

GAMS/Cplex Jun 14, 2002 WIN.CP.CP 20.7 022.024.040.VIS For Cplex 7.5
Cplex 7.5.0, GAMS Link 22

Proven optimal solution.

MIP Solution:	0.451327	(1752 iterations, 701 nodes)
Final LP:	0.451327	(0 iterations)

Best integer solution possible:	0.451327
Absolute gap:	0.000000

Relative gap:	0.000000
---------------	----------

**** REPORT SUMMARY : 0 NONOPT

```

0 INFEASIBLE
0 UNBOUNDED

```

Page 19

General Algebraic Modeling System
Execution

```

---- 715
=====
---- 716 Problem solution with NORM-1 OBJECTIVE AND TWO CUTS
---- 717
=====
719 VARIABLE obj.L = 0.45132657 the objective function

---- 720 VARIABLE epsilonp.L the property slack variable

tcli 0.02650945, pcli 0.27023855, vcli 0.04961692
tbli 0.00820363, wli 0.01482588, solpar 0.08193215

721 VARIABLE nlg.L = 5.00000000 the total number of first order groups

---- 721 VARIABLE n1.L the number of first order groups

1 2.00000000, 23 1.00000000, 26 1.00000000, 33 1.00000000

722 VARIABLE nrings.L = 0.00000000 the total number of rings introduced

---- 722 VARIABLE naromatic.L = 0.00000000
---- 722 VARIABLE yaromatic.L = 0.00000000

---- 723 PARAMETER ft the target value for a property

tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2

---- 723 VARIABLE f.L the properties computed for the mix of groups

tcli 27.72060000, pcli 0.07933600, vcli 0.44036000
tbli 8.24510000, wli 1.95913000, solpar 4.943900E+2

725 VARIABLE elhs.L = 8.00000000 the lhs of the edges equation

---- 725 VARIABLE erhs.L = 8.00000000 the rhs of the edges equation

```

Page 20

General Algebraic Modeling System
Model Statistics SOLVE grouplnorm2 Using MINLP From line 735

MODEL STATISTICS

BLOCKS OF EQUATIONS	16	SINGLE EQUATIONS	134
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	1321	NON LINEAR N-Z	6
DERIVATIVE POOL	10	CONSTANT POOL	8
CODE LENGTH	106	DISCRETE VARIABLES	541
GENERATION TIME	=	0.050 SECONDS	2.1 Mb WIN207-133
EXECUTION TIME	=	0.050 SECONDS	2.1 Mb WIN207-133

Page 21

General Algebraic Modeling System
Solution Report SOLVE grouplnorm2 Using MINLP From line 735


```

      S O L V E      S U M M A R Y

MODEL    group1norm2      OBJECTIVE  obj
TYPE     MINLP            DIRECTION  MINIMIZE
SOLVER   DICOPT           FROM LINE  735

**** SOLVER STATUS      1 NORMAL COMPLETION
**** MODEL STATUS      8 INTEGER SOLUTION
**** OBJECTIVE VALUE    0.0315

RESOURCE USAGE, LIMIT      0.707      1000.000
ITERATION COUNT, LIMIT    1019      1000000
EVALUATION ERRORS         0          0

--- DICOPT: Stopped on NLP worsening

      The search was stopped because the objective function
      of the NLP subproblems started to deteriorate.

-----
Dicopt2x-C      Jun 14, 2002 WIN.DI.DI 20.7 031.024.040.VIS
-----

DICOPT Log File
-----
Major Major      Objective      CPU time      Itera-      Evaluation      Solver
Step  Iter      Function      (Sec)      tions      Errors
NLP   1          0.00195      0.35       77         0         conopt
MIP   1          0.00403      0.07      152         0         cplex
NLP   2          0.03151<      0.01        3         0         conopt
MIP   2          0.00745      0.27      784         0         cplex
NLP   3          0.03173      0.01        3         0         conopt
-----
Total solver times :  NLP =      0.37      MIP =      0.34
Perc. of total      :  NLP =     51.92      MIP =     48.08
-----

**** REPORT SUMMARY :      0      NONOPT
                           0      INFEASIBLE
                           0      UNBOUNDED
                           0      ERRORS

Page 22
General Algebraic Modeling System
Execution

----      740
=====
----      741 Problem solution with NORM-2 OBJECTIVE WITHOUT CUTS
----      742
=====
744 VARIABLE obj.L          =      0.03151002 the objective function

----      745 VARIABLE epsilonp.L the property slack variable

tcli  0.15668669,      pcli  0.00932734,      vcli  0.05222834
tbli  0.15337341,      wli   0.01344804,      solpar 0.10931729

746 VARIABLE nl.g.L =      6.00000000 the total number of first order groups

----      746 VARIABLE n1.L the number of first order groups

1  3.00000000,      7  1.00000000,      19 1.00000000,      26 1.00000000

```

```

747 VARIABLE nrings.L = 0.00000000 the total number of rings introduced
---- 747 VARIABLE naromatic.L = 0.00000000
---- 747 VARIABLE yaromatic.L = 0.00000000
---- 748 PARAMETER ft the target value for a property
tcli 27.00471986, pcli 0.10871498, vcli 0.46335000
tbli 8.17801062, wli 1.98861294, solpar 5.385114E+2
---- 748 VARIABLE f.L the properties computed for the mix of groups
tcli 31.23600000, pcli 0.10972900, vcli 0.48755000
tbli 9.43230000, wli 1.96187000, solpar 5.973800E+2
750 VARIABLE elhs.L = 10.00000000 the lhs of the edges equation
---- 750 VARIABLE erhs.L = 10.00000000 the rhs of the edges equation

```

Page 23

General Algebraic Modeling System
Model Statistics SOLVE group1norm2cut1 Using MINLP From line 780

MODEL STATISTICS

BLOCKS OF EQUATIONS	17	SINGLE EQUATIONS	135
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	1841	NON LINEAR N-Z	6
DERIVATIVE POOL	10	CONSTANT POOL	8
CODE LENGTH	106	DISCRETE VARIABLES	541
GENERATION TIME	=	0.060 SECONDS	2.1 Mb WIN207-133
EXECUTION TIME	=	0.070 SECONDS	2.1 Mb WIN207-133

Page 24

General Algebraic Modeling System
Solution Report SOLVE group1norm2cut1 Using MINLP From line 780

S O L V E S U M M A R Y

MODEL	group1norm2cut1	OBJECTIVE	obj
TYPE	MINLP	DIRECTION	MINIMIZE
SOLVER	DICOPT	FROM LINE	780
**** SOLVER STATUS	1	NORMAL COMPLETION	
**** MODEL STATUS	8	INTEGER SOLUTION	
**** OBJECTIVE VALUE		0.0273	
RESOURCE USAGE, LIMIT	1.892	1000.000	
ITERATION COUNT, LIMIT	7419	1000000	
EVALUATION ERRORS	0	0	

--- DICOPT: Stopped on NLP worsening

The search was stopped because the objective function
of the NLP subproblems started to deteriorate.

Dicopt2x-C Jun 14, 2002 WIN.DI.DI 20.7 031.024.040.VIS

DICOPT Log File

Major Step	Major Iter	Objective Function	CPU time (Sec)	Iterations	Evaluation Errors	Solver
NLP	1	0.00195	0.11	74	0	conopt
MIP	1	0.00407	0.09	302	0	cplex
NLP	2	2.99799<	0.02	3	0	conopt
MIP	2	0.00474	0.17	421	0	cplex
NLP	3	0.44185<	0.01	3	0	conopt
MIP	3	0.00573	0.28	1107	0	cplex
NLP	4	0.05466<	0.01	3	0	conopt
MIP	4	0.00638	0.54	2420	0	cplex
NLP	5	0.02727<	0.01	3	0	conopt
MIP	5	0.00745	0.64	3080	0	cplex
NLP	6	0.03173	0.01	3	0	conopt
<hr/>						
Total solver times :			NLP = 0.17	MIP = 1.72		
Perc. of total :			NLP = 9.08	MIP = 90.92		
<hr/>						

Page 25

General Algebraic Modeling System
Solution Report SOLVE group1norm2cut1 Using MINLP From line 780

```
**** REPORT SUMMARY :      0      NONOPT
                           0      INFEASIBLE
                           0      UNBOUNDED
                           0      ERRORS
```

Page 26

General Algebraic Modeling System
Execution

```
----      785
=====
----      786 Problem solution with NORM-2 OBJECTIVE WITH ONE CUT
----      787
=====
789 VARIABLE obj.L              = 0.02726935 the objective function

----      790 VARIABLE epsilon.L the property slack variable

tcli  0.18041958,    pcli  0.08247234,    vcli  0.01463257
tbli  0.10178385,    wli   0.00505732,    solpar 0.06772114

791 VARIABLE nl.L = 6.00000000 the total number of first order groups

----      791 VARIABLE n1.L the number of first order groups

1  1.00000000,    2  2.00000000,    7  2.00000000,    20 1.00000000

792 VARIABLE nrings.L = 0.00000000 the total number of rings introduced

----      792 VARIABLE naromatic.L          = 0.00000000
----      792 VARIABLE yaromatic.L          = 0.00000000

----      793 PARAMETER ft the target value for a property

tcli  27.00471986,    pcli  0.10871498,    vcli  0.46335000
tbli  8.17801062,    wli   1.98861294,    solpar 5.385114E+2

----      793 VARIABLE f.L the properties computed for the mix of groups

tcli  31.87690000,    pcli  0.09974900,    vcli  0.45657000
```

```

tbli      9.01040000,      wli      1.99867000,      solpar 5.749800E+2
795 VARIABLE elhs.L      =      10.00000000 the lhs of the edges equation
---- 795 VARIABLE erhs.L =      10.00000000 the rhs of the edges equation

```

Page 27

General Algebraic Modeling System
 Model Statistics SOLVE group1norm2cut2 Using MINLP From line 827

MODEL STATISTICS

BLOCKS OF EQUATIONS	18	SINGLE EQUATIONS	136
BLOCKS OF VARIABLES	18	SINGLE VARIABLES	666
NON ZERO ELEMENTS	2361	NON LINEAR N-Z	6
DERIVATIVE POOL	10	CONSTANT POOL	8
CODE LENGTH	106	DISCRETE VARIABLES	541
GENERATION TIME	=	0.050 SECONDS	2.1 Mb WIN207-133
EXECUTION TIME	=	0.050 SECONDS	2.1 Mb WIN207-133

Page 28

General Algebraic Modeling System
 Solution Report SOLVE group1norm2cut2 Using MINLP From line 827

S O L V E S U M M A R Y

MODEL	group1norm2cut2	OBJECTIVE	obj
TYPE	MINLP	DIRECTION	MINIMIZE
SOLVER	DICOPT	FROM LINE	827

```

**** SOLVER STATUS      1 NORMAL COMPLETION
**** MODEL STATUS       8 INTEGER SOLUTION
**** OBJECTIVE VALUE          0.0214

```

RESOURCE USAGE, LIMIT	4.517	1000.000
ITERATION COUNT, LIMIT	19825	1000000
EVALUATION ERRORS	0	0

--- DICOPT: Stopped on NLP worsening

The search was stopped because the objective function
 of the NLP subproblems started to deteriorate.

 Dicopt2x-C Jun 14, 2002 WIN.DI.DI 20.7 031.024.040.VIS

DICOPT Log File

Major Step	Major Iter	Objective Function	CPU time (Sec)	Iterations	Evaluation Errors	Solver
NLP	1	0.00195	0.06	38	0	conopt
MIP	1	0.00407	0.14	306	0	cplex
NLP	2	2.99799<	0.01	3	0	conopt
MIP	2	0.00474	0.17	462	0	cplex
NLP	3	0.44185<	0.01	3	0	conopt
MIP	3	0.00573	0.32	1192	0	cplex
NLP	4	0.05466<	0.01	3	0	conopt
MIP	4	0.00745	0.74	3508	0	cplex
NLP	5	0.03173<	0.01	3	0	conopt
MIP	5	0.00996	1.13	6005	0	cplex
NLP	6	0.02144<	0.01	3	0	conopt

MIP	6	0.02144	0.94	4155	0	cplex
NLP	7	0.02144<	0.01	3	0	conopt
MIP	7	0.02144	0.94	4138	0	cplex
NLP	8	0.02144	0.01	3	0	conopt

Total solver times : NLP = 0.13 MIP = 4.38

Page 29

General Algebraic Modeling System
Solution Report SOLVE group1norm2cut2 Using MINLP From line 827

Perc. of total : NLP = 2.94 MIP = 97.06

**** REPORT SUMMARY : 0 NONOPT
 0 INFEASIBLE
 0 UNBOUNDED
 0 ERRORS

Page 30

General Algebraic Modeling System
Execution

```

----      832
=====
----      833 Problem solution with NORM-2 OBJECTIVE WITH TWO CUTS
----      834
=====
836 VARIABLE obj.L           = 0.02144009 the objective function

----      837 VARIABLE epsilon.L the property slack variable

tcli  0.05410092,    pcli  0.16124713,    vcli  0.07553685
tbli  0.02617866,    wli  0.06016609,    solpar 0.06278160

838 VARIABLE nlq.L = 5.00000000 the total number of first order groups

----      838 VARIABLE n1.L the number of first order groups

1  1.00000000,    5  1.00000000,    7  1.00000000,    20 1.00000000
26 1.00000000

839 VARIABLE nrings.L      = 0.00000000 the total number of rings
introduced

----      839 VARIABLE naromatic.L           = 0.00000000
----      839 VARIABLE yaromatic.L           = 0.00000000

----      840 PARAMETER ft the target value for a property

tcli  27.00471986,    pcli  0.10871498,    vcli  0.46335000
tbli  8.17801062,    wli  1.98861294,    solpar 5.385114E+2

----      840 VARIABLE f.L the properties computed for the mix of groups

tcli  28.46570000,    pcli  0.09118500,    vcli  0.42835000
tbli  8.39210000,    wli  2.10826000,    solpar 5.723200E+2

842 VARIABLE elhs.L      = 8.00000000 the lhs of the edges equation

----      842 VARIABLE erhs.L = 8.00000000 the rhs of the edges equation

```

EXECUTION TIME = 0.000 SECONDS 1.6 Mb WIN207-133

Page 31
G e n e r a l A l g e b r a i c M o d e l i n g S y s t e m
E x e c u t i o n

**** FILE SUMMARY

INPUT
C:\WINDOWS\GAMSDIR\FIRST_ORDER_GROUP_MOLECULAR_DESIGN\BASIC_DEVELOPME
NT_4_JAN_2004\ETHYL GLYCOL ACETATE SET 1.GMS
OUTPUT C:\WINDOWS\GAMSDIR\ETHYL GLYCOL ACETATE SET 1.LST

Chapter 4

Solvent design for crystallization of pharmaceutical products

Arunprakash T. Karunanithi & Luke E.K.Achenie

*Department of Chemical Engineering, University of Connecticut, Storrs, CT-06269
USA*

4.1 INTRODUCTION

The solvent industry is one of the biggest and most important chemical industries. The product of this industry namely ‘solvent’ plays an important role at some stage of the manufacturing chain in the industries that this book deals with. In the pharmaceutical industry solvents are used to facilitate synthetic reactions, enable separation of the product through extraction or crystallization and preparation of final drug formulation. In the agrochemical industry solvents play a key role in the controlled release and delivery of pesticides, herbicides and insecticides to their respective targets. In the paint and coating industry solvents are used to dissolve or disperse various components such as pigments and resins and then evaporate after the application to produce a coat. In the cosmetic industry solvents are used to dissolve ingredients and allow them to work properly. In printing industry solvents are used to control viscosity and assist in optimal drying. It is clear that solvents are either required for processing after which they are removed or they are part of the final product formulation. Figure 1 shows an approximate estimate of various industries that use solvents. (European solvents group: <http://www.esig.info/>)

Solvents are substances that are liquid under the conditions of application and in which other substances can dissolve, and from which they can be recovered unchanged on removal (Marcus, 1998). Solvents for different applications need to have different set of properties with the one common property being its ability to dissolve the substance under consideration. These properties can be broadly classified as performance related properties, physicochemical

properties, environmental properties and safety related properties. Selection of solvents for a particular purpose would be based on one or more of these properties. Some examples of performance related properties are: a) For extraction processes the solvent needs to have high selectivity for the solute, high distribution coefficient between the two compounds being separated, low solvent loss. b) For crystallization processes the solvent should have high potential recovery of crystals. c) For paint formulations the solvent should have high volatility for ease of drying. Some examples of physicochemical properties are boiling and melting point requirements, viscosity, density and thermal conductivity. Typical environmental properties are lethal concentration (LC50), octanol water partition coefficients, bioconcentration factor and permissible exposure limit (PEL). A typical safety related property is flash point. In certain instances we might have to consider hard to quantify properties such as odor and color.

Solvents can be classified into three categories according to their polarity namely, polar protic, dipolar aprotic and non-polar. Most of the common solvents fall under one of following chemical classes: Aliphatic hydrocarbons, aromatic hydrocarbons, alcohols, phenols, ethers, aldehydes, ketones, carboxylic acids, esters, halogen-substituted hydrocarbons, amines, nitriles, nitro-derivatives, amides and sulfur-containing solvents (Marcus, 1998). In certain cases a mixture of two or more solvents would perform better than a single solvent.

In this chapter we present case studies relevant to the pharmaceutical industry. Specifically we consider the design of crystallization solvents for pharmaceuticals. In the manufacture of many pharmaceuticals, the high molecular weight chemicals are recovered as pure solids from impure solutions via crystallization. One of the key decisions in designing solution crystallization processes is the selection of solvents. This chapter describes a systematic approach involving computer aided molecular design (CAMD) technique, for solvent design/selection for crystallization of pharmaceuticals. Two case studies relating to the design of solvents for ibuprofen, an important pharmaceutical compound, are presented. The first case study involves cooling crystallization solvent design while the second case study involves design of solvent/antisolvent mixture for drowning out crystallization. An experimental verification step is also presented for the ibuprofen cooling crystallization solvent design problem

Section 2 gives a detailed description of the solvent design problem that is being addressed, section 3 describes a decomposition-based computer aided molecular

design (CAMD) methodology we recently proposed (Karunanithi et al., 2005), which is being used to solve the solvent design problem while section 4 describes the two case studies (Karunanithi et al., 2005b).

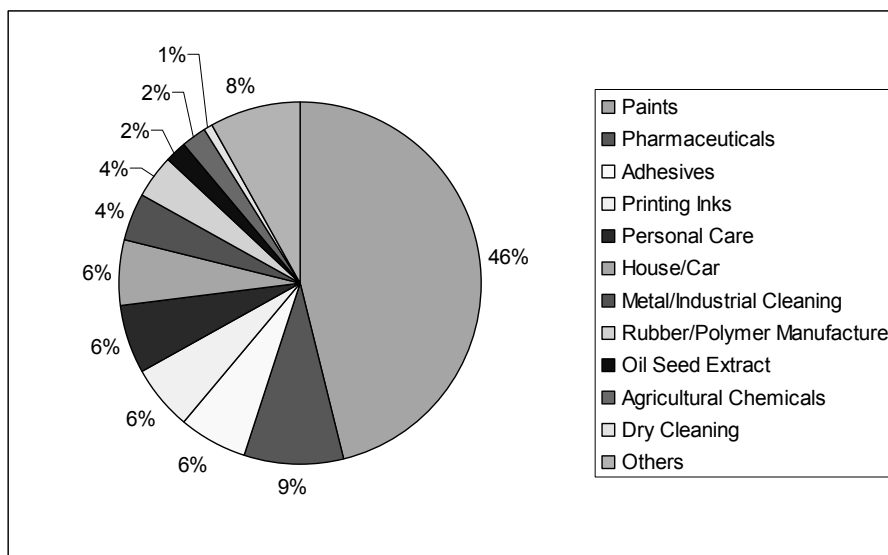


Figure 1: Distribution of solvent consumption by various industries

4.2 CRYSTALLIZATION SOLVENT DESIGN

Within the chemical process industry, crystallization is one of the key unit operations in the production of high value chemicals. Crystallization from solution is widely used for the purification of drugs during the final stages of manufacture. Design/selection of the optimal solvent for a given crystallization operation is not trivial. Nass (1994) describes a strategy for choosing crystallization solvents based on equilibrium limits. Frank et al., (1999) review strategies for solvent selection for various types of crystallization processes such as cooling crystallization and drowning out crystallization. However solvent selection for crystallization process involves tradeoffs between numerous properties such as solubility, potential recovery of crystals, solvent effect on crystal morphology, solvent inflammability, solvent toxicity etc., which needs to be considered during design and selection. This section describes the various properties that are important for crystallization solvent design. The section also presents the group contribution models that can be used to estimate those properties.

4.2.1 Solubility

The solvent should have high solubility for the solute being crystallized. The capacity of the solvent to solvate can be quantitatively assessed through its solubility parameter value. Under the ‘like dissolves like’ paradigm, a non-polar solute is generally more soluble in a non-polar solvent. Hence a solvent with solubility parameter value close to that of the solute can be assumed to have high solubility for the solute. The following empirical equation can be used to estimate the solubility parameter

$$Sol.Par. = \left[\frac{1000 * H_{298}^{vap} - R * T}{V_{298}^m} \right]^{1/2} \quad (1)$$

Here H_{298}^{vap} and V_{298}^m can be estimated using the Constantinou-Gani group contribution method (Constantinou and Gani, 1994).

4.2.2 Potential Recovery

A good solvent for crystallization should have high solubility for the solute as well as high potential recovery. This means that the solvent for cooling crystallization should be such that it should have high solubility for the solute at a high temperature, and relatively low solubility at a low temperature (i.e. high temperature coefficient of solubility). Initial solubility determines the size of the crystallizer, while the temperature coefficient of solubility determines the yield. In the case of drowning out crystallization the solvent should have high solubility for the solute, while the solubility should decrease greatly when the anti-solvent is added. Eqn’s 2 and 3 can be used to evaluate the potential recovery for cooling and drowning out crystallizations respectively (Frank et al., 1999).

$$PR\% = \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2} \right) \quad (2)$$

X_1 and X_2 are weight fraction solubilities at high and low temperatures respectively.

$$PR\% = \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2} \left(1 + \frac{M_{as}}{M_T} \right) \right) \quad (3)$$

Note that in Eqn. 3, X_1 and X_2 are evaluated at the same temperature. M_{as} and M_T are mass of anti-solvent and total mass respectively.

The solubility values are functions of pure component properties of the solute ($\Delta H_{fus}, T_m$) and the liquid phase activity coefficients of the components in solution. Solubility is calculated using the following equation

$$\ln x_i^{Sat} - \frac{\Delta_{fus} H}{T_m} \left(1 - \frac{T_m}{T} \right) + \ln \gamma_i^{Sat} = 0 \quad (4)$$

The liquid phase activity coefficient, which is a function of the subgroups, composition and temperature, can be evaluated using the UNIFAC group contribution method (Freedunslund et al., 1975).

4.2.3 Crystal Morphology

The morphology of a crystal is defined as the type of external shape that results from the different rates of growth of the various faces (Mullin, 1961). The type of solvent being used for crystallization can affect the morphology of the product crystals. For example, Naphthalene crystallizes in the form of needles from cyclohexane and as thin plates from methanol (Mullin, 1961). Crystal morphology influences downstream processing such as filtering, washing, drying, packaging, handling and storage. Crystal morphology also plays a role in the quality and efficacy of solid dose pharmaceuticals, where crystals of different shapes have different bioavailabilities. Crystal morphology also affects the ease with which the crystals are compressed into tablets (as in drugs). Usually, for pharmaceutical products crystals having lower aspect ratio (ratio between the two major dimensions of the crystal) are preferred.

Davey et al., 1982, have shown that succinic acid crystals grown from aqueous solution are plate shaped while those grown from isopropanol are needle shaped. Gordon and Amin, 1984 have studied the modification of ibuprofen crystal shapes using solvents with varying hydrogen bonding properties. Either this knowledge or some preliminary experimentation would enable us to consider this property in the design. In this chapter we use the constraint on hydrogen bonding solubility parameter, to account for crystal morphology. The following equation was used to estimate the hydrogen bonding solubility parameter

$$\delta_H = \sum_i \sum N_i \delta_{hi} / V_m^{298} \quad (5)$$

where the molar volume V_m^{298} is evaluated using a group contribution model (ICAS, 2003).

4.2.4 Toxicity of the Solvent

Toxicity of the solvent is one of the key criteria in the design of crystallization solvents. Almost all organic solvents are toxic to some extent when their vapor is inhaled or when they are injected. Also traces of solvents could be present in the final product and hence particularly for pharmaceuticals, toxicity of the solvent being used is a key criterion. In this study, $-\log(\text{LC50})$ is considered as a quantitative measure of the toxicity. LC50 represents the aqueous concentration causing 50% mortality in fathead minnow after 96 hours. The higher the value of $-\log(\text{LC50})$, the more toxic the compound is. Even though this study was based on mortality of fathead minnow it is a good quantitative measure of the level of toxicity of the designed solvents. $-\log(\text{LC50})$ values can be evaluated using the group contribution method of Martin and Young, 2001.

$$-\log(\text{LC}_{50}) = \sum_i N_i \alpha_i \quad (6)$$

4.2.5 Flammability Limit of the Solvent

Flash point is one of the most important fire safety characteristics and hence it is a very important consideration in solvent design. The flammability limit of a solvent is characterized by its flash point, which is the temperature at which the mixture of air and vapor above the liquid can be ignited (Mullin, 1961). It is the lowest point at which the vapor pressure of a liquid will produce a flammable mixture. The flash point of the solvent can be estimated using the following group contribution method (ICAS, 2003)

$$T_f = 3.63 * \sum_i \sum N_i T_{fi} + 0.409 * T_b + 8843 \quad (7)$$

where,

$$T_b = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \quad (8)$$

4.2.6 Viscosity of the Solvent

The performance of many process equipment encountered in crystallization practice is often profoundly affected by the flow properties of the liquid media. Heat transfer, for example, may be severely impeded in ‘thick’ sluggish liquors or magmas; crystallization may occur only with difficulty, and filtration and washing of crystalline product may be impaired (Mullin, 1961). Since viscosity is a function of temperature the viscosity at the average temperature of crystallization is considered. The viscosity of the solvent can be estimated using the following group contribution model (ICAS, 2003)

$$\mu = \text{Molecularweight} * 1000 * \text{EXP} \left(\sum_i N_i \mu_i / T + \sum_j M_j \mu_j \right) \quad (9)$$

4.2.7 Liquid State of the Solvent

The solvents should be in the liquid state under the operating conditions defined by temperature and liquid composition of solution. To ensure this, limits on boiling points and melting points of the solvents need to be imposed. The boiling point and melting point can be estimated using the Constantinou and Gani group contribution model. (Constantinou and Gani, 1994)

$$T_m = 102.425 * \sum_i N_i T_{mi} + \sum_j M_j T_{mj} \quad (10)$$

$$T_b = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \quad (11)$$

4.3 PROBLEM SOLUTION

The crystallization solvent design problem is solved using the Computer aided molecular design (CAMD) technique. CAMD is a reverse engineering approach, which generates molecules with specific properties. The most common approach in CAMD is to computationally generate chemically feasible molecular structures from a set of descriptors (represented by fragments or building blocks) and to test them by estimating their desired properties (Achenie et al., 2004). Computer aided molecular design (CAMD) can be defined as ‘given a set of building blocks and a specified set of target properties, determine the molecule or molecular structure that matches these properties.’ More details about CAMD and various solution approaches for CAMD can be found elsewhere (Achenie et al., 2004). In this chapter we use a decomposition-based CAMD methodology (Karunanithi et al., 2005). In this methodology the generic

molecule-mixture design CAMD problem is formulated as a mixed integer non-linear programming (MINLP) optimization model. This model is then decomposed into an ordered set of sub-problems. Each sub-problem (except the final) only requires the solution of a sub-set of the constraints from the original set. The final sub-problem contains the objective function and the remaining constraints.

4.3.1 *Problem Formulation as a MINLP Model*

The general CAMD problem can be formulated as a mixed integer non-linear programming (MINLP) problem, where a (process/ product) performance index is optimized subject to constraints (molecular structural constraints, molecular property constraints, mixture property constraints, process models etc.). Structural constraints are molecular generation rules that need to be satisfied to form a structurally feasible molecule from a collection of groups or descriptors. In most of the CAMD problems the constraints for the combination rules of the groups proposed by Odele and Machietto, 1993 or Churi and Achenie, 1996 are used. Pure component properties required for CAMD, such as normal melting point, normal boiling point, solubility parameter etc. can be evaluated using group contribution techniques, which are based on molecular structure information. New group contribution methods, which consider higher order groups (Constantinou and Gani, 1994; Marrero and Gani, 2001), improve the accuracy of the property prediction. The mixture property that is of importance in many CAMD applications related to liquid solvents is the liquid phase activity coefficient from which properties such as solubility can be evaluated. The UNIFAC group contribution method (Fredenslund et al., 1975) is used for prediction of activity coefficients. Process models usually consist of mass-energy balance equations, constitutive equations (property models) and constraint equations (such as phase equilibrium relationships). All these process model related equations can be represented as equality constraints.

Considering the various types of constraint equations, a general CAMD problem (Molecular and Mixture design) can be formulated as the following MINLP.

$$\begin{aligned}
 &\text{Min/Max } f_{obj}(X, Y), \\
 &\text{subject to} \\
 &\quad \text{Structural constraints : } g_1(Y) \leq 0, \\
 &\quad \text{Pure component property constraints : } g_2(Y) \leq 0, \\
 &\quad \text{Mixture property constraints : } g_3(X, Y) \leq 0, \\
 &\quad \text{Process model constraints : } g_4(X, Y) = 0.
 \end{aligned}$$

Y is a vector of binary variables (integer), which are related to the identities of the building blocks (groups, descriptors) and/or molecules. X is a vector of continuous variables, which are related to the mixture (*e.g.*, compositions) and/or process variables (*e.g.*, flow rates, temperatures *etc.*). f_{obj} is the performance objective function, defined in terms of molecule/mixture-process (performance) characteristics and/or cost that may be minimized or maximized. g_1 and g_2 are sets of structural constraints (related to feasibility of molecular structure) and pure component property constraints (related to properties-molecular structure relationships) respectively. g_3 and g_4 are mixture property (related to properties-mixture relationships) constraints and process model (related to process-molecule/mixture relationships) constraints respectively. Usually g_1 and g_2 are linear in their arguments.

4.3.2 Decomposition Based Solution Methodology

The constraints in the general CAMD problem are first decomposed into two parts, namely pure component design part and mixture design part as shown in Figure 2. If we are interested in single compound solvent design, only the first part is needed while if we are interested in mixture design both parts are needed.

4.3.2.1 Single compound design

The single compound CAMD problem is decomposed into four sub-problems

(a) Sub-problem 1

This sub-problem considers the structural constraints that result in generation of feasible molecular structures. Odele & Machietto structural feasibility constraints are used. The sub-problem is a function of the binary variables alone.

(b) Sub-problem 2

This sub-problem considers the pure component properties. This sub-problem is also a function of binary variables alone (because these constraints only handle primary structure based properties). The feasible molecular structures from Sub-problem 1 are solved for the pure component properties. Those molecules, which satisfy the pure component property constraints, are then passed into sub-problem 3.

(c) Sub-problem 3

This sub-problem considers the mixture properties. Mixture properties can be categorized into two types. Properties such as selectivity, solvent power etc., are based on infinite dilution activity coefficients, which are independent of composition and hence only structural information is needed for their calculation. Properties such as complete or partial miscibility of solvent with another constituent is handled by discretizing the composition range from 0 to 1 into 'n' divisions and verifying the miscibility criterion at those points. The difference between pure component property constraints and mixture property constraints is that the former are linear and the latter are non-linear. Those satisfying the mixture property constraints are further analyzed in sub-problem 4.

(d) Sub-problem 4

In sub-problem 4 the process model constraints (function of both integer and continuous variables) are considered along with the objective function. The optimal solvent is identified by either solving a smaller MINLP problem (if the number of feasible solutions is large) or a set of NLP problems (if the number of feasible solutions is small) by fixing the values of integer variables.

4.3.2.2 Mixture design

The mixture design CAMD problem is also solved as a series of sub-problems. Here promising pure component solvents are designed first and then candidate solvent mixtures are identified. The first three sub-problems deal with the design of pure component solvents.

(a) Sub-problem 1^M

As in sub-problem 1 structural constraints are considered in sub-problem 1^M. All the feasible molecular structures are passed to sub-problem 2^M.

(b) Sub-problem 2^M

Sub-problem 2^M considers the pure component property constraints where the compounds from sub-problem 1^M are evaluated for the pure component properties. All the molecules satisfying these constraints are passed onto sub-problem 3^M.

(c) Sub-problem 3^M

Sub-problem 3^M considers the mixture property constraints. The molecules from sub-problem 2^M are considered in this sub-problem. The starting point is a list of promising solvents. From this list of solvents, the optimal mixture and the compositions of the constituents are identified by solving sub-problem 4^M and sub-problem 5^M. Since the first three sub-problems in the mixture design involves designing pure component solvents, these sub-problems are essentially the same as the first three sub-problems in single compound design.

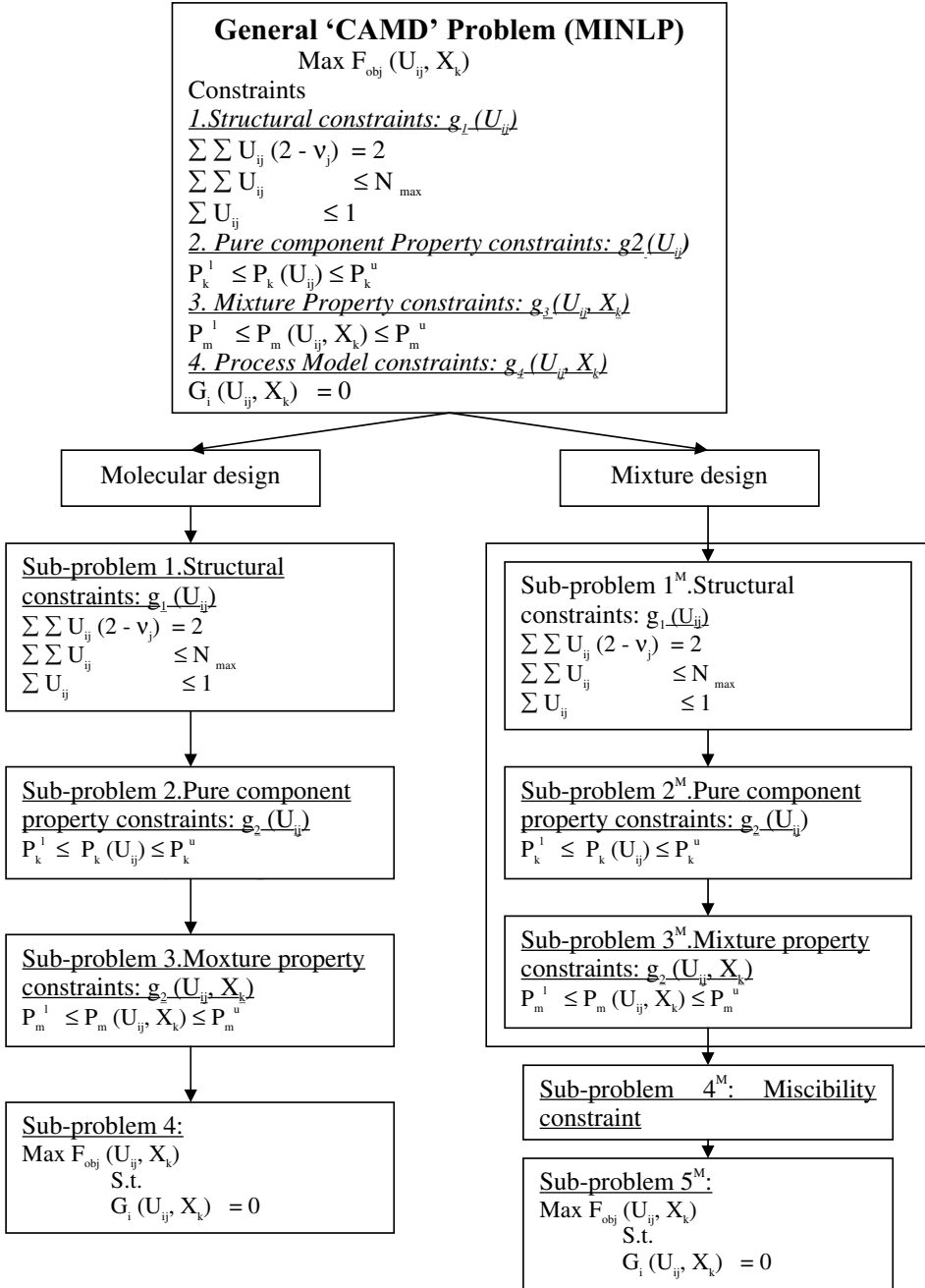
(d) Sub-problem 4^M

In sub-problem 4^M the miscibility of the solvents among themselves in the mixture (e.g. miscibility of two solvents if a binary mixture is designed) is considered.

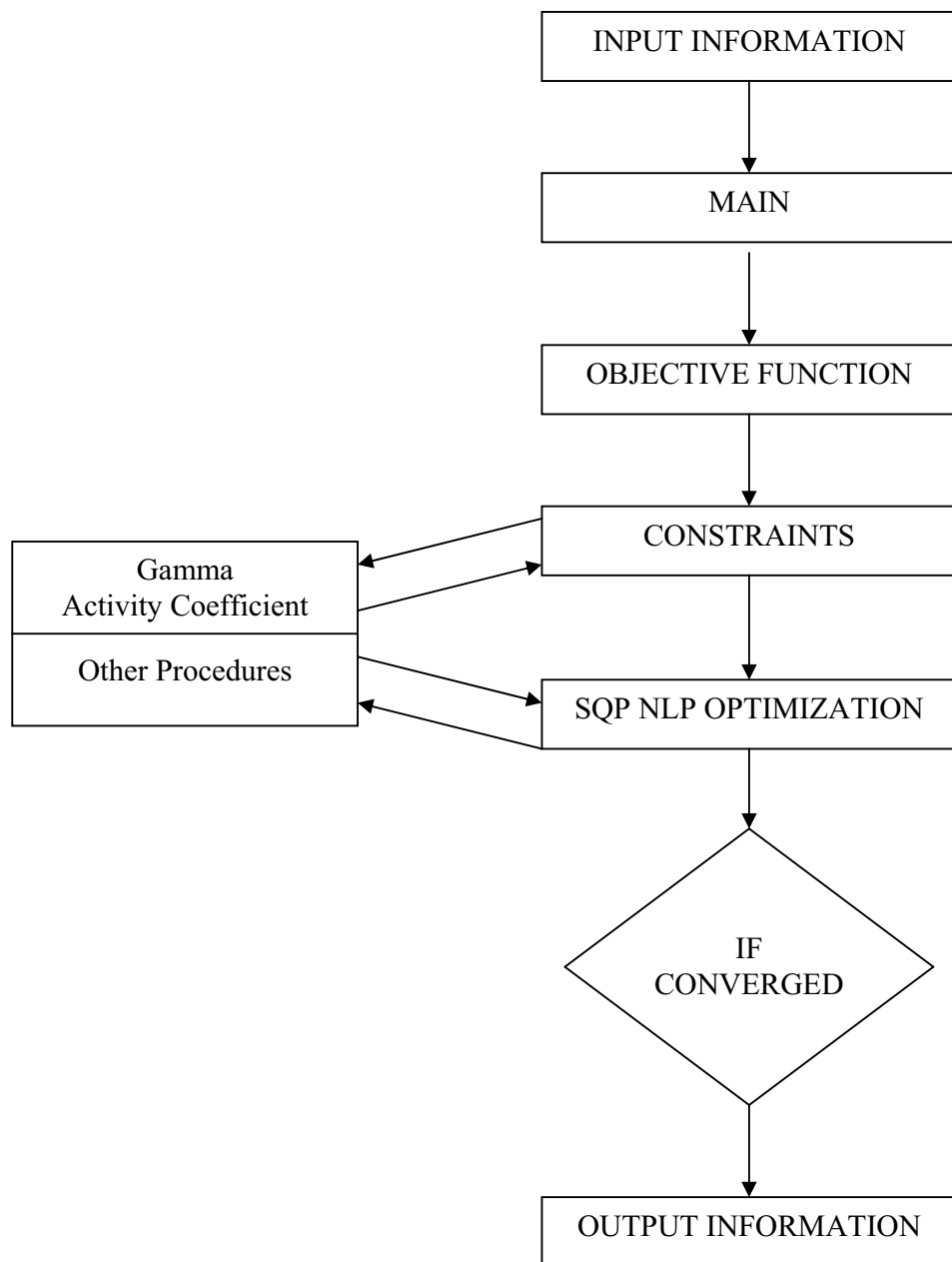
(e) Sub-problem 5^M

In sub-problem 5^M the process model constraints are considered along with the objective function and the optimal mixture is identified by solving a smaller MINLP problem (if the number of feasible solutions is large) or a set of NLP problems (if the number of feasible solutions is small).

In some mixture design problems (such as formulations), it may not be necessary to consider processing issues and hence we would not have the process model constraints. In this case the problem becomes a simple mixing problem, which would already have been addressed by the miscibility criteria in sub-problem 4^M. Hence, for these problems, we will not need sub-problem 5^M. Also in some cases we might have to identify a mixture whose constituents perform different functions such as solvents and anti solvents for crystallization. In such cases we would have to formulate and solve more than one single compound design problems to identify the constituents and then solve the final two sub-problems to identify the optimal mixture. In certain cases we may not have process model constraints, however, we may still have to solve an optimization problem with other constraints, in sub-problem 4 and sub-problem 5^M respectively.

Figure 2: Flow diagram of OPT-CAMD⁺

The requirements for the methodology are an algorithm to generate molecular structures (sub-problem 1 & 1^M), an algorithm for evaluating the various pure component properties, mixture properties and to screen the feasible structures (sub-problems 2, 3, 2^M, 3^M) and an algorithm for the solution of the final optimization problem (sub-problem 4 or sub-problem 5^M). In the case of mixture design we need an additional step to verify the miscibility criterion (sub-problem 4^M). The methodology is implemented in two linked parts. The tools employed in these two parts are ProCAMD (ICAS documentation. Internal report, 2003) and OPT-CAMD⁺. Molecule generation and property evaluations are carried out in ProCAMD while the optimization part is carried out in OPT-CAMD⁺. ProCAMD uses a multi level algorithm for generation of molecular structure and property predictions (see Harper et al., 2002). In ProCAMD constraints can be provided for 26 non-temperature dependent pure component properties, 6 temperature dependent pure component properties and 9 mixture properties. Also miscibility calculation can be performed. The results of ProCAMD are fed into OPT-CAMD⁺, which solves the final optimization part, where the performance index is optimized subject to the process model constraints. OPT-CAMD⁺ uses sequential quadratic programming (SQP) algorithm for solving the NLP optimization problem. The flowchart of OPT-CAMD⁺ algorithm is shown in Figure 3. Data flow diagrams for single compound design and mixture design are shown in Figures 4 and 5 respectively.

**Figure 3:** Flow diagram of OPT-CAMD⁺

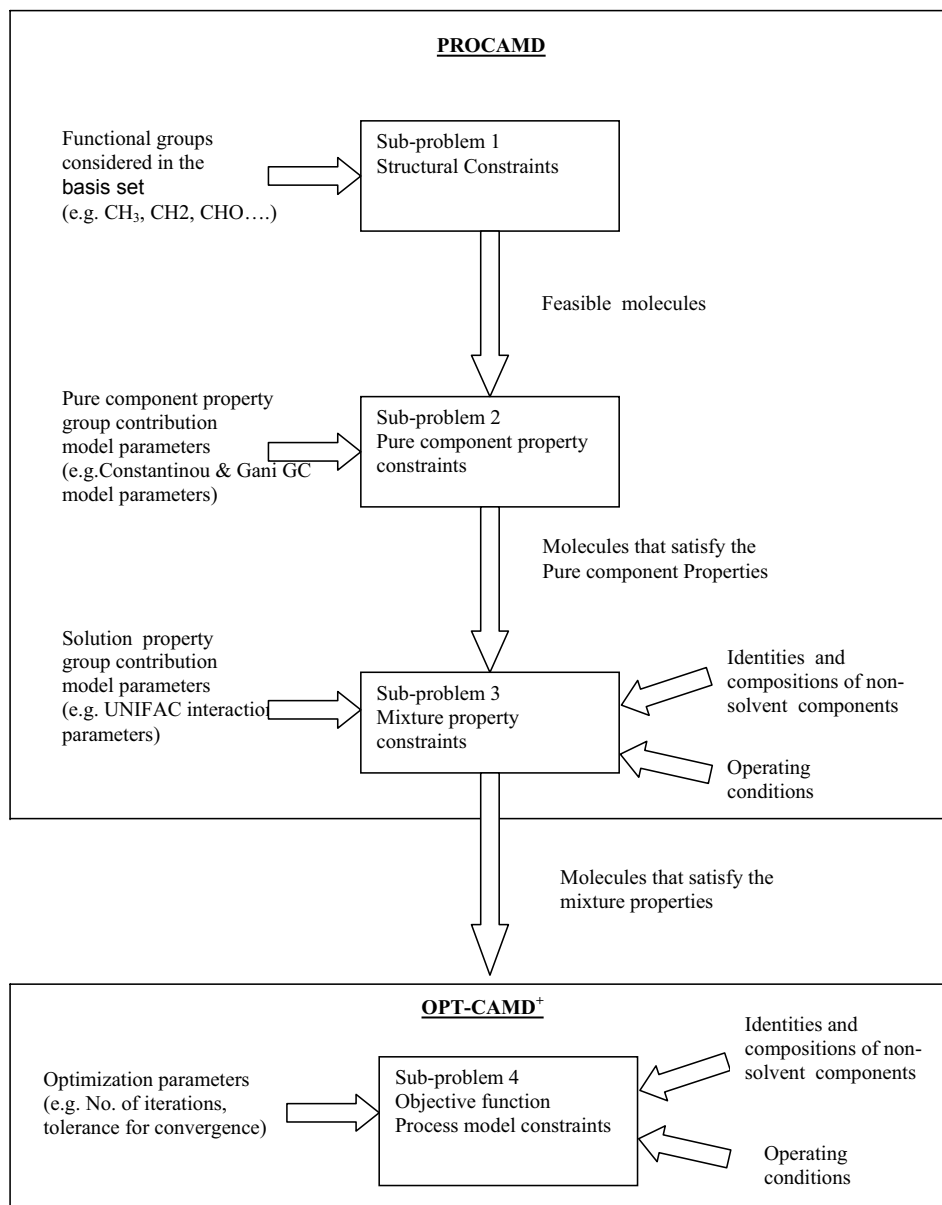


Figure 4: Dataflow diagram- Single compound design

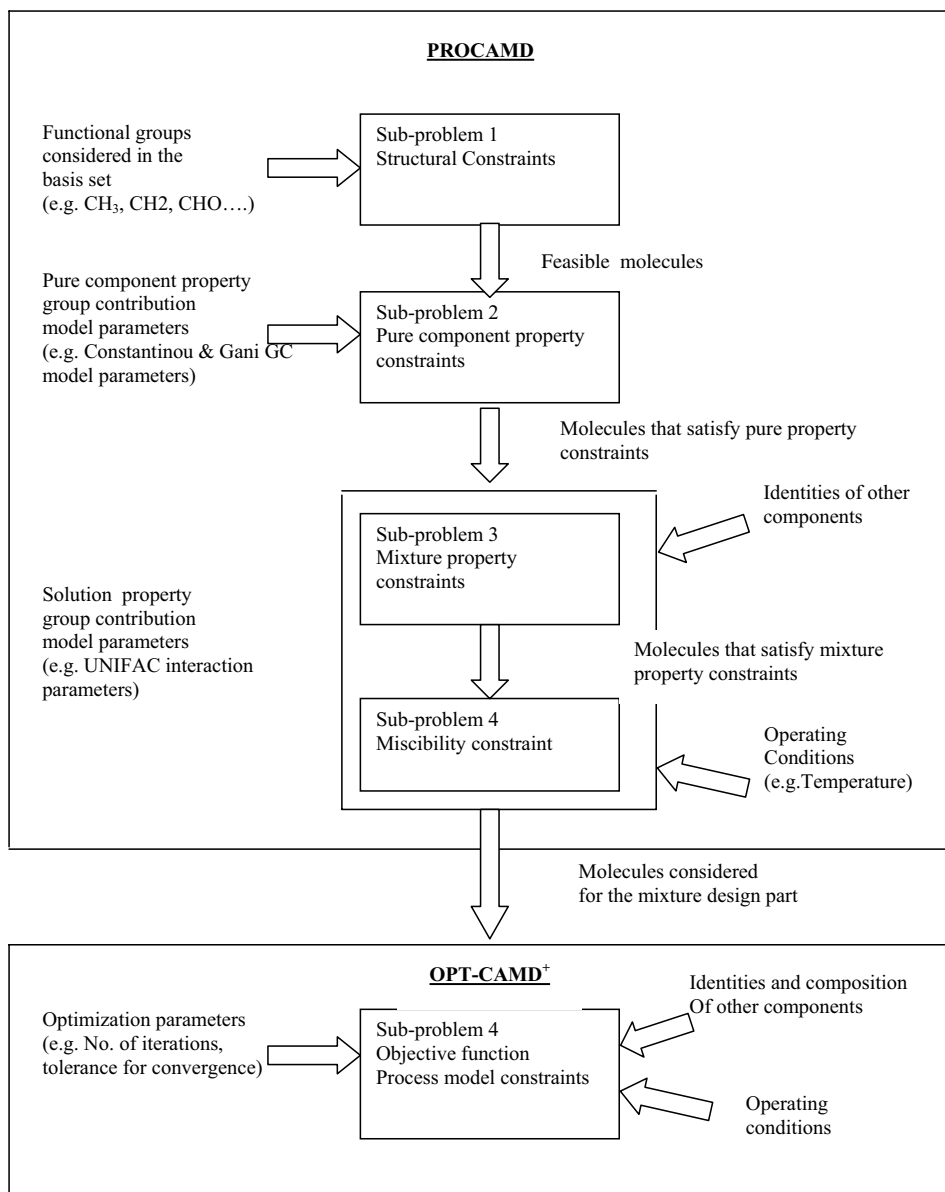


Figure 5: Dataflow diagram- Mixture design

4.4 CASE STUDIES

In this section we present two case studies that involve the design of solvents for ibuprofen, a very well known anti-inflammatory drug used to relieve pain, stiffness and inflammation caused by arthritis and grout. It is also used to reduce fever and relieve headaches, muscle aches, backache, and aches from cold. The IUPAC name of ibuprofen is 2-(4-Isobutyl-phenyl)-propionic acid and has a structure as shown in Figure 6. Ibuprofen is a colorless, crystalline solid having a melting point of 350 K. It is relatively insoluble in water and soluble in most organic solvents. Ibuprofen is crystallized commercially by cooling crystallization with heptane or hexane as solvents (Gordon and Amin, 1984). A commercial form of ibuprofen is Advil. The objective in the first case study is to design a suitable solvent for crystallization of ibuprofen, through cooling crystallization method. The objective of the second case study is to design a solvent/anti-solvent mixture for crystallization of ibuprofen, through drowning out crystallization method. In both of the case studies first we describe the formulation of the design problem as an MINLP model and then describe the solution of the model through the decomposition methodology and finally we describe the verification of the design results.

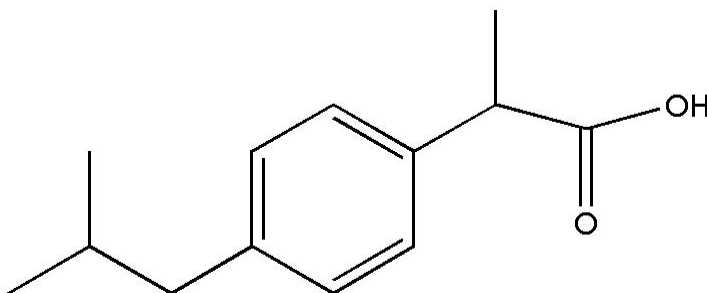


Figure 6: Ibuprofen structure

4.4.1 Case Study 1: Cooling Crystallization Solvent Design

A batch cooling crystallization is one of the most commonly used crystallization method. In this process super saturation of a liquid is achieved by means of a cooling process. The solubility of the solute (in the solvent) decreases with a decrease in temperature; this leads to precipitation of the solute.

4.4.1.1 Problem formulation

This CAMD single compound problem is formulated as an MINLP model as shown below. The performance objective function and the various property constraints in the model are discussed subsequently.

$$\text{Max } PR\% = \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2}\right) \quad (12)$$

$$\sum_i \sum_j u_{ij} (2 - v_j) = 2 \quad (13)$$

$$\sum_i \sum_j u_{ij} = N_{\max} \quad (14)$$

$$\sum_j u_{ij} = 1 \quad (15)$$

$$17 \leq \delta \leq 19 \text{ MPA}^{1/2} \quad (16)$$

$$\delta_H \geq 8 \text{ MPA}^{1/2} \quad (17)$$

$$T_f = 3.63 * \sum_i \sum_j N_i T_{fi} + 0.409 * T_b + 8843 \geq 323 \text{ K} \quad (18)$$

$$- \text{Log}(LC_{50}) \leq 3.3 \quad (19)$$

$$T_m = 102.425 * \sum_i N_i T_{mi} + \sum_j M_j T_{mj} \leq 270 \text{ K} \quad (20)$$

$$T_b = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \geq 340 \text{ K} \quad (21)$$

$$\mu \leq 1 \text{ cp} \quad (22)$$

$$\ln x_i^{\text{Sat}} - \frac{\Delta_{fus} H}{T_m} \left(1 - \frac{T_m}{T}\right) + \ln \gamma_1^{\text{Sat}} = 0 \quad (23)$$

$$x_1 + x_2 = 1 \quad (24)$$

$$260 \leq T \leq 320 \quad (25)$$

1. *Potential recovery*: The objective is to maximize the potential recovery of ibuprofen crystals and this is posed as the objective function. The potential recovery for cooling crystallization is estimated using Eqn 12.

2. *Solubility parameter*: The solubility parameter value of ibuprofen estimated by the Marrero and Gani group contribution method (Marrero and Gani, 2001) is $17 \text{ Mpa}^{1/2}$. To ensure design of solvents having high solubility for ibuprofen we enforce the following constraint on the solubility parameter of the solvent

$$17 \leq \delta \leq 19 \text{ Mpa}^{1/2}$$

3. *Crystal morphology*: Ibuprofen crystals from hexane or heptane are characteristically rod or needle shaped. Gordon and Amin (1984) report that ibuprofen having better physical properties than previously known crystalline ibuprofen materials. They state that ibuprofen crystallized from a solution containing a substantial amount of any solvent which has a hydrogen bonding solubility parameter (δ_H) equal or greater than $8 \text{ Mpa}^{1/2}$, results in ibuprofen crystals having larger particle size, substantial drop in bulk volume, static charge for the particles, faster dissolution rate properties, reduced sublimation rate and excellent manufacturability as compared to crystalline ibuprofen obtained from hexane or heptane. The equant shaped crystals produced from a solvent having $\delta_H > 8 \text{ Mpa}^{1/2}$ had excellent flow characteristics with a average length to width aspect ratio of 4:1 as opposed to small acicular (needle) or lath (blade) shaped crystals obtained from heptane or hexane having an aspect ratio of 6:1. To ensure ibuprofen crystals having higher aspect ratio we enforce the following constraint on the hydrogen bonding solubility parameter of the solvent.

$$\delta_H \geq 8 \text{ Mpa}^{1/2}$$

3. *Inflammability*: To ensure stringent constraints on inflammability the following constraint in flash point is enforced.

$$T_f \geq 323 \text{ K}$$

4. *Toxicity*: The following constraint is imposed on the designed solvent to ensure low toxicity (-Log LC_{50}) of the organic solvent.

$$- \text{Log}(LC_{50}) \leq 3.3$$

6. *Liquid range of solvent*: The solvent should be in the liquid state near the operating conditions. To ensure this following limits on boiling point and melting point are placed.

$$T_b \geq 340 \text{ K}$$

$$T_m \leq 270 \text{ K}$$

7. *Viscosity of the solvent*: An upper limit of 1 Cp is placed on the viscosity of the designed solvent.

$$\mu \leq 1 \text{ Cp}$$

Eqn's 13, 14 and 15 represent the structural constraints; Eqn's 23 and 24 represent the solid liquid equilibrium and mole fraction constraints respectively. The UNIFAC sub-groups that were used to generate the molecules are given in the appendix.

4.4.1.2 Problem solution

The CAMD problem formulated as an MINLP model was solved using the decomposition approach and the results are presented below

Sub-problem 1

The three structural constraints (Eqn's 13, 14 and 15) are considered in sub-problem 1. Here 2691 molecules are generated.

Sub-problem 2

The seven pure component properties (Eqn's 16, 17, 18,19,20,21 and 22) are considered in sub-problem 2. Out of the 2691 molecules from sub-problem 1, 10 molecules satisfied these constraints. One of the compounds 2-ethoxy ethyl acetate was found in the CAPEC database (ICAS, 2003).

Sub-problem 3

Since we do not have any mixture property constraints related to single compound design this sub-problem was ignored.

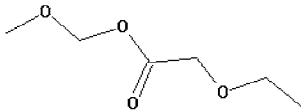
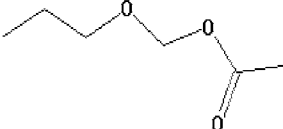
Sub-problem 4

The optimization problem solved in sub-problem 4 is shown below.

$$\begin{aligned}
 \text{Max } PR\% &= \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2}\right) \\
 \text{Subject to} \\
 \ln x_i^{\text{Sat}} - \frac{\Delta_{\text{fus}} H}{T_m} \left(1 - \frac{T_m}{T}\right) + \ln \gamma_1^{\text{Sat}} &= 0 \\
 x_1 + x_2 &= 1 \\
 260 \leq T \leq 320
 \end{aligned}$$

The above problem becomes an NLP problem when we fix the integer variables and since we have only 10 feasible compounds, 10 NLP problems were solved by fixing the binary variables representing the 10 compounds. Sequential quadratic programming algorithm was used to solve the NLP problems. The molecular structure and design results of the optimal solvent and 2-ethoxy ethyl acetate are shown in Table 1.

Table 1: Design results of optimal solvent and 2-ethoxy ethyl acetate

Molecular Structure	 Optimal solvent	 2-ethoxy ethyl acetate
%Potential recovery	89.927	89.07
Solubility parameter	18.36 MPA ^{1/2}	18.56 MPA ^{1/2}
Hydrogen bonding solubility parameter	9.43 MPA ^{1/2}	8.48 MPA ^{1/2}
Flash point	354.29 K	330.10
-log (LC50)	3.04	3.28
Normal melting point	235.23 K	218.77K
Normal boiling point	450.96 K	424.83K
Viscosity	0.993 cp	0.865 cp

4.4.1.3 Verification through solid liquid equilibrium diagrams

The performance, in terms of ability to dissolve ibuprofen is compared for the optimal solvent found in this work, the solvent commonly used (n-hexane) and a compound known to have low solubility for ibuprofen (ethylene glycol). Figure 7 shows the plots of the solid (ibuprofen) saturation curves as a function of temperature, calculated under SLE conditions. The plots provide a visual confirmation of the performance of the optimal solvent and the importance of the selection of the locations for X1 and X2. It can be noted from the plots that ethylene glycol has a very low solubility for ibuprofen and it is not suitable as a solvent. Note that ethylene glycol has a solubility parameter value of 33 MPa^{1/2} and hence it does not satisfy the solubility parameter constraint (Eqn.16) in our problem formulation thereby making it infeasible. It seems n- hexane is a good solvent for ibuprofen and it would have a higher potential recovery than the optimal solvent since it has much lower solubility at lower temperature as compared to the optimal solvent. However, note that n-hexane has an estimated hydrogen bonding solubility parameter value close to 0 MPa^{1/2} and hence it does not satisfy the hydrogen bonding solubility parameter constraint (Eqn. 17) in our problem formulation thereby making it infeasible. Also, Gordon and Amin, 1984 give experimental proof that ibuprofen crystals grown from n-hexane are needle shaped. The optimal solvent satisfies all the constraints and has good solubility (as well as potential recovery) for ibuprofen.

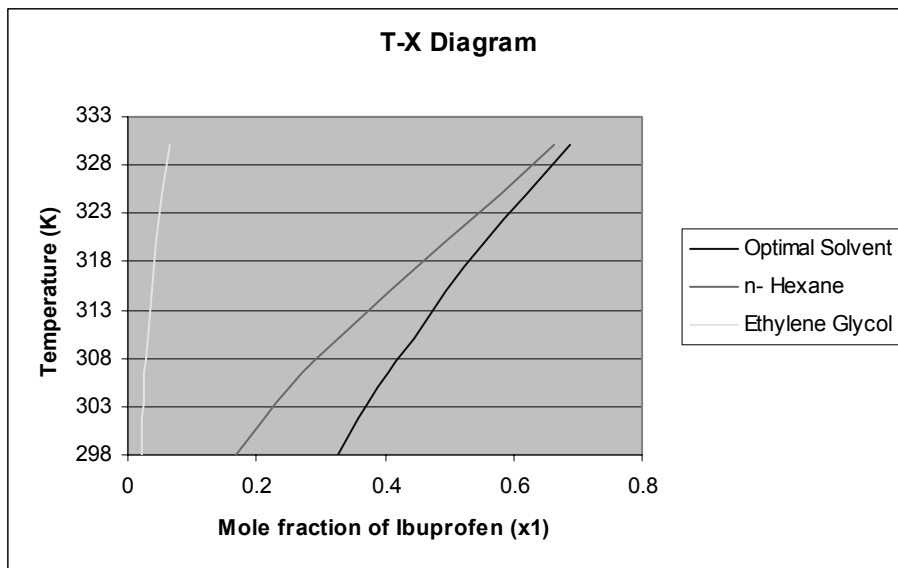


Figure 7: SLE diagram

4.4.1.4 Experimental verification of crystal morphology

In this section the performance of the designed solvent with regards to crystal morphology is verified experimentally. For verification by experiments, 2-ethoxy ethyl acetate was selected since it is an already existing solvent, and since it is one among the top 10 compounds, its properties are bound to be very similar to the properties of the optimal compound. However if we can synthesis the optimal solvent molecule, then it could also have been used in the experimental verification.

A suitable amount of ibuprofen was dissolved in 5 ml of solvent at 40⁰ C. Excess ibuprofen was added after saturation was reached at that temperature. Then the temperature was raised to 60⁰ C. Precipitation was reached by cooling to 20⁰ C over a period of 120 minutes, and then kept at that temperature overnight to allow maximum recovery of crystals. The obtained crystals were collected by filtration under vacuum condition and dried in a desiccator under vacuum. The solvents used were 2-ethoxy ethyl acetate (modeling result) and n-hexane. n-hexane was used for the purpose of comparison.

Scanning electron micrographs of crystals were taken using a scanning electron microscope. Samples were fixed on an aluminum stub. The specimens were mounted on a metal stub with double-sided adhesive tape and coated under vacuum condition with gold in an argon atmosphere using a sputter coater, prior to observation. The SEM micrographs of crystals grown from 2-ethoxy ethyl acetate and n-hexane are shown in the Figures 8 and 9 respectively. We can observe that the morphology of the crystals grown from 2-ethoxy ethyl acetate (high hydrogen bonding solubility parameter) has lower aspect ratio, while the morphology of the crystals grown from n-hexane (low hydrogen bonding solubility parameter) has higher aspect ratio.

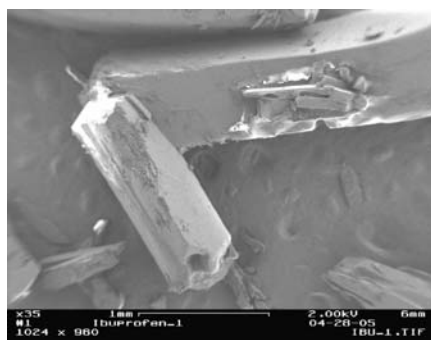


Figure 8: Ibuprofen crystallized from 2-ethoxy ethyl acetate



Figure 9: Ibuprofen crystallized from n-hexane

4.4.2 Case study 2: Drowning-out Crystallization Solvent Design

Cooling crystallization, where the driving force is the difference in solubility at different temperatures may not always be the feasible mode of crystallization. In some cases the solute may decompose at higher temperatures, and hence cooling crystallization is not a suitable option for heat sensitive materials. Cooling crystallization is also not suitable for compounds whose solubility changes relatively little with temperature. Other reasons when cooling crystallization is not suitable are (a) if the solute reacts with solvent at higher temperature (could affect yield) and, (b) if impurities are formed at higher temperatures (could affect purity). These issues are highly prevalent in the manufacture of pharmaceuticals, where drowning out crystallization is used. In this method the driving force is the difference in solubility created by the addition of a poor solvent called anti-solvent to the solution. In some cases the anti-solvent is completely miscible with the mother liquor at all process conditions. In other cases the anti-solvent is miscible with solvent during crystallization but immiscible at other temperatures, thereby facilitating separation of solvent from anti-solvent. The design and selection of suitable solvent and anti-solvent is the most important step in the design of drowning-out crystallization process.

The potential recovery for a simple drowning out crystallization involving no solvent evaporation can be estimated using Eqn.3. Since the total mass of the batch increases as anti-solvent is added, the potential recovery may go through a maximum, with the values beginning to decline after a certain amount of anti-solvent is added (Frank et al., 1999). This of course depends upon how much the solubility of solute changes on addition of anti-solvent. Hence the design problem becomes the identification of the optimal solvent/anti-solvent pair as well as the optimal composition corresponding to the maximum potential recovery.

4.4.2.1 Problem formulation

This CAMD mixture design (solvent/anti-solvent) problem is formulated as an MINLP model as shown below. The objective function and the various property constraints in the model are discussed subsequently

$$\text{Max } PR\% = \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2} \left(1 + \frac{M_{as}}{M_T} \right) \right) \quad (26)$$

Subject to

$$\sum_i \sum_j u_{ij} (2 - v_j) = 2 \quad (27)$$

$$\sum_i \sum_j u_{ij} = N_{\max} \quad (28)$$

$$\sum_j u_{ij} = 1 \quad (29)$$

$$T_m(\text{solvent}) = 102.425 * \sum_i N_i T_{mi} + \sum_j M_j T_{mj} \leq 270 \text{ K} \quad (30)$$

$$T_b(\text{solvent}) = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \geq 340 \text{ K} \quad (31)$$

$$T_f(\text{solvent}) = 3.63 * \sum_i \sum_j N_i T_{fi} + 0.409 * T_b + 8843 \geq 323 \text{ K} \quad (32)$$

$$17 \leq \delta(\text{solvent}) \leq 19 \text{ MPa}^{1/2} \quad (33)$$

$$T_f(\text{anti-solvent}) = 3.63 * \sum_i \sum_j N_i T_{fi} + 0.409 * T_b + 8843 \geq 323 \text{ K} \quad (34)$$

$$T_b(\text{anti-solvent}) = 204.359 * \sum_i N_i T_{bi} + \sum_j M_j T_{bj} \geq 340 \text{ K} \quad (35)$$

$$T_m(\text{anti-solvent}) = 102.425 * \sum_i N_i T_{mi} + \sum_j M_j T_{mj} \leq 270 \text{ K} \quad (36)$$

$$\delta(\text{anti-solvent}) \geq 30 \text{ MPa}^{1/2} \quad (37)$$

$$\frac{1}{x_2} + \frac{\partial \ln \gamma_2}{\partial x_2} \geq 0 \quad (38)$$

$$\ln x_i^{\text{Sat}} - \frac{\Delta_{fus} H}{T_m} \left(1 - \frac{T_m}{T} \right) + \ln \gamma_1^{\text{Sat}} = 0 \quad (39)$$

$$x_1 + x_2 + x_3 = 1 \quad (40)$$

In the above MINLP model, the potential recovery is the objective function (Eqn. 26) subject to other property and phase equilibrium constraints (Eqn's. 27-40). The decisions that need to be made are the identities of the solvent and anti-solvent (binary variables) and the composition of solvent and anti-solvent

(continuous variables, x_1 and x_2) corresponding to the maximum value of the objective function.

Since in this mixture design problem we have to identify a mixture whose constituents perform different functions, i.e., the solvent needs to have high solubility for the solute while the anti-solvent needs to reduce the solubility, we have to solve two different single compound design problems (involving sub-problem 1^M, 2^M and 3^M) to identify the candidate solvents and anti-solvents. The mutually miscible pairs are identified in sub-problem 4^M and the final optimisation problem is solved in sub-problem 5^M.

The structural constraints used in the first case study namely, Eqn's 27,28 and 29 are used again. The melting point, boiling point and flash point, are used as constraints for both solvent and anti-solvent. Since the solvent needs to have high solubility for solute and the anti-solvent needs to have low solubility for the solute limits of $17 \leq \delta \leq 19$ and $\delta \geq 30$ (Eqn's. 33 and 37) are placed on the solubility parameters of solvent and anti-solvents respectively. Eqn.38 gives the necessary condition for phase stability (Bernard et al., 1967), which needs to be satisfied for the solvent-anti solvent pairs to be miscible with each other. Eqn. 39 gives the solid-liquid equilibrium constraint.

4.4.2.2 Problem solution

This problem encompasses two single compound CAMD problems, namely design of solvent and anti-solvent and then identification of optimal mixture pair and its composition. The single component solvent design problem is the same as in case study 1 (Sub-problems 1, 2 and 3). The 10 molecules that are designed in the first case study are considered here. The single component anti-solvent design proceeds as follows

Sub-problem 1^M

Since these constraints are the same, the same 2691 molecular structures generated for the single compound solvent design are generated in sub-problem 1.

Sub-problem 2^M

The four pure component properties for anti-solvents (Eqn's 34,35,36 and 37) are considered in sub-problem 2. Out of the 2691 molecular structures, 5 satisfied these constraints. Note that these 5 anti-solvents are different from the 10 solvents identified before.

Sub-problem 3^M

Since we do not have any mixture property constraints related to single compound anti-solvent design this sub-problem was ignored.

Now we have 10 solvents and 5 anti-solvents, which satisfy their respective constraints. The optimal pair of solvent/anti-solvent and their mixture compositions is identified with the help of sub-problems 4^M and 5^M.

Sub-problem 4^M

The miscibility of solvent anti-solvent pairs is considered in sub-problem 4^M through constraint represented by Eqn.38. Only 6 pairs were found to be mutually miscible with each other.

Sub-problem 5^M

The optimization problem to be solved in sub-problem 5^M is shown below.

$$\begin{aligned} \text{Max } PR\% &= \frac{100}{1 - X_1} * \left(1 - \frac{X_1}{X_2} \left(1 + \frac{M_{as}}{M_T} \right) \right) \\ \text{Subject to } \ln x_i^{Sat} - \frac{\Delta_{fus} H}{T_m} \left(1 - \frac{T_m}{T} \right) + \ln \gamma_1^{Sat} &= 0 \\ x_1 + x_2 + x_3 &= 1 \end{aligned}$$

The above problem becomes an NLP problem when we fix the integer variables. Since we have only 6 feasible pairs, 6-NLP problems were solved by fixing the binary variables representing the solvent and anti-solvent in the 6 pairs. The molecular structures of the optimal solvent and anti-solvent mixture giving a maximum potential recovery of 69% ibuprofen is shown in Table 2. The properties of solvent and anti-solvent are shown in Table 3 and Table 4 respectively.

Table 2: Design results of optimal solvent-anti solvent mixture for drowning out crystallization

Component	Structure	Compositions
Solvent		0.21
Anti-solvent		0.89

Table 3: Design results of optimal solvent for drowning out crystallization

Solubility parameter	33.37 MPa ^{1/2}
Hydrogen bonding solubility parameter	26.21 MPa ^{1/2}
Flash point	446.35 K
-log (LC50)	-1.18
Normal melting point	269.74 K
Normal boiling point	524.43 K

Table 4: Design results of optimal anti-solvent for drowning out crystallization

Solubility parameter	18.23 MPa ^{1/2}
Hydrogen bonding solubility parameter	8.74 MPa ^{1/2}
Flash point	341.55 K
-log (LC50)	3.26
Normal melting point	243.2 K
Normal boiling point	445.28 K

4.4.2.3 Verification through solid-liquid equilibrium diagram

Figure 10 shows the SLE T-X diagram for ibuprofen-optimal solvent (1), ibuprofen- solvent/ anti-solvent mixture (2) and ibuprofen- solvent/ dimethyl formamide mixture. In the case of the mixtures the binary plots are plotted with x_1 being the composition of ibuprofen and x_2 being the sum of compositions of solvent/anti-solvent and solvent/dimethyl formamide. This is done to visually show the qualitative behavior of solvent/anti-solvent. Plot 1 is the SLE curve for pure solvent. Plots 2 and 3 are SLE curves in the presence of 50% solvent and 50 % anti-solvent. For a given temperature solvent/anti-solvent mixture curve should be as far away (to the left) as possible from the original curve (1) in order to achieve high recovery. Curve 2 shows that dimethyl formamide is a very poor anti-solvent because it is not able to move the curve very much. On the other hand the optimal anti-solvent is able to move the curve significantly to the left from the initial curve. The solvent and anti-solvent mixture shows, at least qualitatively, that the desired process behavior is obtained.

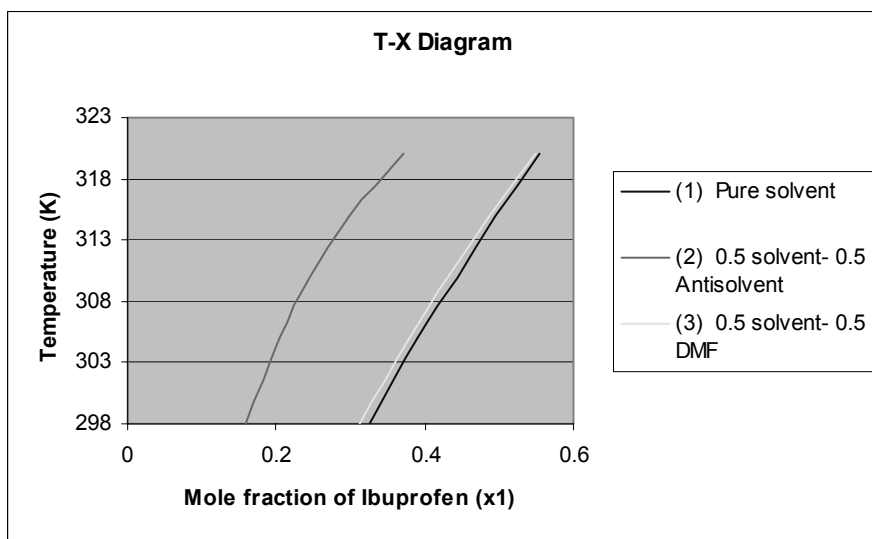


Figure 10: SLE diagram

4. 5 CONCLUSIONS

This chapter provides a framework for the design of crystallization solvents for pharmaceutical products. The design part involves application of a

decomposition-based computer-aided molecular design approach to generate solvents having desired crystallization related properties. Two case studies related to cooling crystallization and drowning out crystallization are presented. Theoretical and experimental verification of the design results are also presented. Since the design results can be viewed as identifying suitable candidates for which further experiments should be done, an experimental verification step is also carried out in order to present a complete methodology. In this way, the experimental effort and resources are spent only in the final verification step and not in the trial and error search steps.

ACKNOWLEDGEMENTS

The authors would like to thank CAPEC, Department of Chemical Engineering, Technical University of Denmark, for the use of ICAS software.

NOMENCLATURE

R	Universal gas constant = $0.008314 \text{ KJ} / \text{gmol.K}$
T	Temperature K
H_{298}^{vap}	Heat of vaporization KJ / gmol
V_{298}^m	Molar volume $\text{Cm}^3 / \text{gmol}$
u_{ij}	Binary variable indicating whether the i^{th} position in a molecule has structural group j .
v_j	Valence of group j .
N_{max}	Maximum number of positions in a molecule.
N_i	Number of times the first order group 'i' is present.
M_j	Number of times the second order group 'j' is present
δ	Solubility parameter $\text{MPA}^{1/2}$
δ_H	Hydrogen bonding solubility parameter $\text{MPA}^{1/2}$
δ_{hi}	Contribution of i^{th} group to the hydrogen bonding solubility parameter
T_{bi}	Boiling point K
$T_{bi}^{(i^{\text{th}})}$	Contribution of ' i^{th} ' first order group to the boiling point
$T_{bj}^{(j^{\text{th}})}$	Contribution of ' j^{th} ' second order group to the boiling point
T_m	Melting point K
$T_{mi}^{(i^{\text{th}})}$	Contribution of ' i^{th} ' first order group to the melting point
$T_{mj}^{(j^{\text{th}})}$	Contribution of ' j^{th} ' second order group to the melting point
T_f	Flash point K
$T_{fi}^{(i^{\text{th}})}$	Contribution of ' i^{th} ' first order group to the flash point
$\alpha_i^{(i^{\text{th}})}$	Contribution of ' i^{th} ' group to LC50
μ	Viscosity cp
$\mu_i^{(i^{\text{th}})}$	Contribution of ' i^{th} ' first order group to viscosity

μ_j	Contribution of 'j th ' second order group to viscosity
$\Delta_{fus}H$	Heat of fusion <i>KJ / gmol</i>
γ_i	Liquid phase activity coefficient of component 'i'
x_i	Mole fraction of component 'i'

REFERENCES

1. Achenie, L.E.K., Gani, R., Venkatasubramanian, V. (2003). Computer aided molecular design: theory and practice. Elsevier, Amsterdam.
2. Bernard, G.; Hocine, R.; Lupis, C.H.P. Thermodynamic conditions for spinodal decomposition in a multicomponent system. *Transactions of the metallurgical society of AIME*. 1967, 239, 1600-1604.
3. Churi, N., Achenie, L.E.K., (1996). Novel mathematical programming model for computer aided molecular design. *Ind. Eng. Chem. Res.*, 35(1), 3788-3794.
4. Constantinou, L., Gani, R., (1994). New Group-contribution method for estimating properties of pure compounds. *AIChE J.*, 40(10), 1697-1710.
5. Davey, R.J., Whiting, M.J.L., (1982). Habit modification of succinic acid crystals grown from different solvents. *Journal of Crystal Growth.*, 58, 304-312.
6. Frank, T.C., Downey, J.R., Gupta, S.K. (1999). Quickly screen solvents for organic solids. *Chem. Eng. Prog.*, 95 (12), 41-61.
7. Fredenslund, A., Jones, R.L., Prausnitz, J.M., (1975). Group -contribution estimation of activity coefficients in nonideal liquid mixtures. *AIChE J.*, 21(6), 1086.
8. Gordon, R.E., Amin, S.I., (1984). Crystallization of Ibuprofen, U.S. Patent number 4,476,248.
9. Harper, P.M., Gani, R., Kolar, P., Ishikawa, T., (1999). Computer-aided molecular design with combined molecular modeling and group contribution. *Fluid Phase Equilib.*, 158-160, 337-347.
10. ICAS documentation. (2003). Internal report, CAPEC, Department of chemical engineering, Technical university of Denmark.
11. Karunanithi, A.T., Achenie, L.E.K., Gani, R., (2005). A new decomposition-based computer aided molecular/mixture design methodology for the design of optimal solvents and solvent mixtures. *Ind. Eng. Chem. Res.*, 44(13), 4785-4797.
12. Karunanithi, A.T., Achenie, L.E.K., Gani, R., (2005b). A computer-aided molecular design framework for crystallization solvent design. *Chemical Engineering Science.*, Accepted for publication.
13. Marcus Y., (1998). The properties of solvents, Wiley series on solution chemistry, Volume 4, Baffins Lane, Chichester.
14. Marrero, J., Gani, R., (2001). Group contribution based estimation of pure component properties. *Fluid Phase Equilib.*, 183.
15. Martin, T.M., Young, D.M., (2001). Prediction of the acute toxicity (96-h LC₅₀) of organic compounds to the fathead minnow (*Pimephales*

- promelas) using group contribution method. *Chem. Res. Toxicol.*, 14, 1378-1385.
16. Mullin, J.W. (1961). *Crystallization*. Butterworths: England.
 17. Nass, K.K., (1994). Rational solvent selection for cooling crystallizations. *Ind. Eng. Chem. Res.*, 33, 1580-1584.
 18. Odele, O., Machietto, S., (1993). Computer aided molecular design: a novel method for optimal solvent selection. *Fluid Phase Equilib.*, 82, 47-54.
 19. Zhao, R., Cabezas, H., (1998). Molecular thermodynamics in the design of substitute solvents. *Ind. Eng. Chem. Res.*, 37, 3268-3280.

APPENDIX

Sub Group	Sub group number	Main group number	Sub Group	Sub group number	Main group number
CH ₃	1	1	CH ₃ COO	22	11
CH ₂	2	1	CH ₂ COO	23	11
CH	3	1	HCOO	24	12
C	4	1	CH ₃ O	25	13
OH	15	5	CH ₂ O	26	13
CH ₃ CO	19	9	CH-O	27	13
CH ₂ CO	20	9	COOH	43	20
CHO	21	10	COO	77	41

Chapter 5

Design of liquid enzyme products with built-in liquid detergent stabilization system

Lone Kierstein Nielsen and Ole Simonsen

Novozymes A/S, DK-2800 Bagsværd, Denmark

5.1 BACKGROUND

Liquid detergents are a large and growing part of the detergent market. Liquid detergents are generally perceived as convenient to use and easy to dose (Lai, 1997). Several classes of enzymes (biological catalysts) are present in both powder and liquid detergents where they assist in the removal of specific stains. E.g. do proteases remove stains such as egg and blood whereas amylases remove starchy stains and lipases remove fat stains such as butter (van Ey et al., 1997).

Enzymes are biological catalysts in the form of globular proteins, and in liquid detergent compositions enzymes have inherent stability problems since the proteases not only digest the protein stains, but also the other enzymes. If this destructive mechanism is not controlled, the enzymes in the liquid detergent composition will have unacceptably short storage stability.

The first choice of enzyme to add to a detergent is practically always a protease. The proteases in modern detergents are subtilisins which are microbial enzymes from *Bacillus*. The subtilisins consist of approximately 270 amino acids and are heart-shaped molecules with a binding cleft and a binding pocket to which substrates such as protein stains can be bound by non-covalent forces.

The molecular weight of these enzymes is around 27,000 g/mol. The active site where the catalysis takes place consists of a catalytic triad of Serine-221, Histidine-64, and Aspartate-32 (the numbers indicates the position of the amino acid in the peptide chain). A model of a subtilisin showing the binding cleft and the amino acids of the catalytic triad is illustrated through Figure 1.

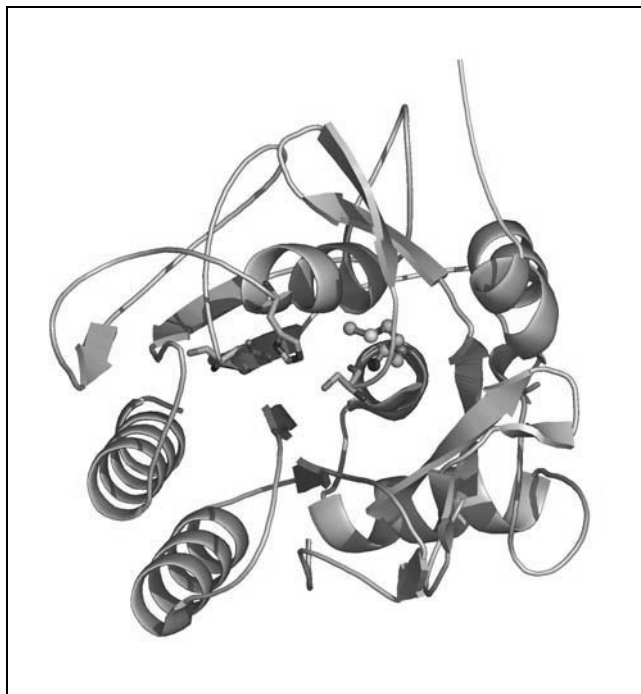


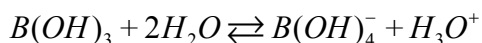
Figure 1. A model of a subtilisin showing the binding cleft and the amino acids of the catalytic triad (Serine-221, Histidine-64, and Aspartate-32)

The catalytic mechanism of the subtilisins is the same as that of the digestive enzymes trypsin and chymotrypsin as well as that of enzymes in the blood clotting cascade, reproduction and other mammalian enzymes. The enzymes are known as serine proteases due to the serine residue which is crucial for catalysis (Kraut, 1977 and Polgar, 1987)

Unlike many other enzymes, the subtilisins are fairly stable towards e.g. organic solvents, anionic surfactants, high temperatures and high pH. This makes the subtilisins very suitable as detergent proteases. But despite this fact, stabilization of these protease enzymes in liquid detergents remains a major issue.

Boric acid has been known to have a stabilizing effect on the enzymes in liquid detergents and has been a component in liquid detergents for many years along with other ingredients such as surfactants, alcohols (e.g. glycerol and propyleneglycol), perfumes and color. Boric acid in combination with polyols is by far the most used enzyme stabilization system for liquid detergents, and a vast number of patents have been issued around this technology (Boskamp, 1992 and Tai, 1982)

Boric acid, $B(OH)_3$ is a Lewis acid with $pK_a = 9.0$. A hydroxyl group is added to the trigonal boric acid molecule forming a tetrahedral borate ion:



In liquid detergents, the boric acid is generally added as Borax, $Na_2B_4O_7 \cdot 10 H_2O$. Borax is dissolved in the liquid detergents and a pH-dependent equilibrium between boric acid and the borate ion is thereby obtained.

The closest organic specie to the inorganic boric acid are the boronic acids generally described as $R-B(OH)_2$. Boronic acids have been shown to act as inhibitors of the subtilisins. X-ray crystallographic studies of phenylboronic acid and phenyl-ethyl-boronic acid adducts with Subtilisin Novo have shown that they contain a covalent bond between the oxygen atom of the catalytic serine of the enzyme and the inhibitor boron atom (Matthews et al, 1975 and Lindquist & Terry, 1974). The boron atom is co-ordinated tetrahedrally in the enzyme inhibitor complex. It is likely that boric acid itself interacts with the active site of the subtilisins in the same manner.

The inhibition constant K_i for the complex between the enzyme (E) and the inhibitor (I) is the dissociation constant for the enzyme inhibitor complex (EI):

$$EI \rightleftharpoons E + I \quad ; \quad K_i = \frac{[E] \cdot [I]}{[EI]}$$

The inhibition constant is thus measured in units of concentration with a low value corresponding to strong inhibition. The inhibition constant for boric acid is approximately 10^{-2} M.

If we combine the equation above with the two mass balances

$$[E_0] = [E] + [EI]$$

and

$$[I_0] = [I] + [EI]$$

where E_0 and I_0 are the total concentrations of enzyme and inhibitor, respectively, we get three equations with the three unknowns $[E]$, $[I]$, and $[EI]$.

If we solve these equations we get:

$$[EI] = \frac{1}{2} \left([E_0] + [I_0] + K_i - \sqrt{([E_0] + [I_0] + K_i)^2 - 4[E_0][I_0]} \right)$$

which allows for calculations of the distribution of the enzyme between free and inhibited enzyme at any combination of K_i , E_0 , I_0 . One may e.g. calculate a range of K_i 's between which the enzyme is practically fully inhibited in the detergent and almost fully liberated in the wash solution due to the large dilution factor which shifts the equation towards the free and active protease.

The concentration of boric acid in the liquid detergent needed to obtain stabilization is typically around 1-3%(w/w). Solubility limits prevents the use of concentrations of boric acid above a few per cent. The relatively high amount of used boric acid makes the detergent formulation more difficult to develop due to solubility problems and components being incompatible with high amounts of boric acid.

Novozymes supplies the proteases for liquid detergents to the detergent manufacturer as a stable liquid enzyme formulation from which typically less than 2%(w/w) is added to the liquid detergent composition. The limited solubility of boric acid thus prevents Novozymes from supplying the detergent manufacturer with a liquid enzyme formulation with a built-in boric acid stabilization system.

5.2 PRODUCT DESIGN PROBLEM FORMULATION

The aim for this product design case was to design a liquid detergent enzyme product, with a built-in stabilization system, making it possible for the user (the liquid detergent designer) to avoid addition of boric acid and reduce the amount of polyols thus saving cost and broadening the product design possibilities. The product should thus be a sound alternative to the current system used in liquid detergents, but delivered as an integrated part of the enzyme formulation.

The design goals for the stabilization system were:

- It must be delivered with/in the enzyme formulation (without decreasing enzyme activity of our products)
- It should be at least as efficient as the current boric acid system
- The cost should be lower than current boric acid/polyol system
- It should be toxicological safe
- It should not jeopardize the quality of the enzyme formulation itself (physical, microbial and enzymatic stability etc.)

5.3 DESIGN METHODOLOGY

To achieve the goals set several technologies were identified that could be investigated:

- Designing more stable enzymes e.g. by genetically engineering
- Micro-encapsulation of enzymes
- Designing more efficient inhibitors

Designing more stable enzyme proteins, e.g. via genetically replacing oxidation labile amino acids with more stable ones, has been followed for several other

products with great success, especially designing enzymes for powder detergents e.g. to improve the stability of enzymes towards bleach in powder detergents (von der Osten et al, 1993). For liquid detergents this would require re-design of several enzyme classes, and in general it is very difficult to protect proteins from being digested by the very potent proteases used in liquid detergents.

Micro-encapsulation of enzymes was developed by Novozymes in parallel to the development of new inhibitors. However, the goal for the micro-encapsulated enzymes was to find a stabilization system that could make enzymes work in detergents where enzymes are not used today, i.e. broadening the market (Ness et al, 2003). The draw-backs for these micro-capsules are that they change the appearance of the detergent by making the detergent hazy and give requirements and thus limitations for the formulation of the liquid detergent.

Designing more efficient inhibitors was judged to be the most obvious way to achieve the goals as the mechanism for the stabilization is the same as for the well-known and proven boric acid system. The similarity to already proven technologies increases the chance of success in this case, where the goal is a direct alternative to an existing and well-functioning system.

Having selected inhibition as the technology the characteristics of a useful inhibitor were set:

- It should be a reversible inhibitor
- It should be at least in the order of 50 times more efficient than boric acid to be possible to incorporate in our enzyme formulation (dependent on the solubility of the inhibitor)
- The equilibrium between enzyme and inhibitor should be obtained fast and upon dilution with water in the wash cycle the inhibitor should release from the protease immediately.
- The inhibitor itself must be stable in liquid detergents

Further the inhibitor according to the goals should be toxicological safe, be cost-effective compared to boric acid and be compatible with Novozymes enzyme formulations.

5.4 CANDIDATE SELECTION

A large number of potential reversible protease inhibitors exist (Laskowski & Kato, 1980). Protein protease inhibitors like Streptomyces Subtilisin Inhibitor (SSI) (Hiromi et al, 1985) and Chymotrypsin Inhibitor (CI-2) (Jonassen, 1980 and McPhalen & James, 1988) are known to be very strong inhibitors with inhibition constants at or below 10^{-10} M.

The above mentioned organic boronic acids were however expected to have approximately the same fast inhibition pattern and stability in liquid detergents as boric acid and again the similarity to the well-known systems was decisive for choosing this technology.

After selecting organic boronic acid inhibitors as our lead candidate technology an industrial partner with knowledge of this chemistry was found. Together with this partner a large number of potential candidates were identified, synthesized and subsequently tested. The selection of these candidates was based on both pragmatic/practical and theoretical considerations. Whatever we could find of readily available boronic acids and other boron components taken off the shelves were tested. From computer models of the structure of our proteases boronic acids were “docked” into the binding pocket giving input to which components we should synthesize. For instance the modeling exercises suggested that inhibitors with three or more rings in the organic moiety would suffer from steric hindrance. Figure 2 shows the docking of 4-formylphenyl boronic acid into the binding pocket of a subtilisin.

5.5 TESTING OF CANDIDATES

The primary selection of candidates was based on the inhibition efficiency. It was chosen to use two different experimental assays for testing the efficiency of the candidate inhibitors:

- Enzyme kinetics and determination of K_i in a buffer system (the inhibitor approach)
- Storage stability trials in model liquid detergent (the stabilizer approach)

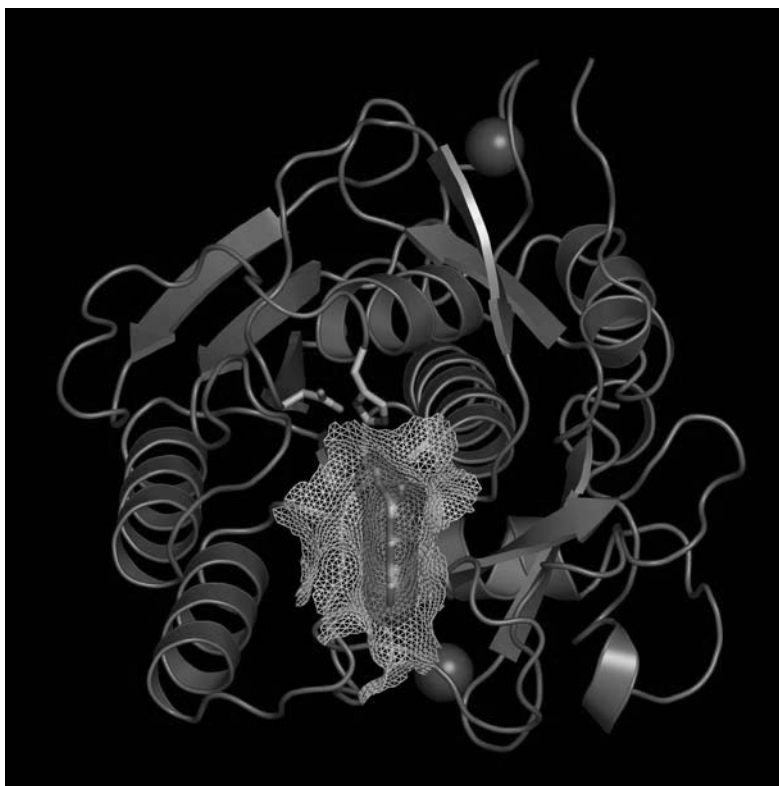


Figure 2: Docking of 4-formylphenyl boronic acid into the binding pocket of a subtilisin

The latter assay is closest to the final application of the inhibitors, but a second different assay was chosen in order to increase the understanding of the boronic acids as inhibitors and also to reduce the risk of false negative results. Boronic acids with promising results in both assays were chosen for further testing, inhibitors with negative result in both assays were rejected while inhibitors with divergent results were re-tested. Fortunately the latter very seldom became necessary. Even though the absolute values of the inhibition constants were not identical in the two assays the ranking of the inhibitors most often was the same. All in all, the correlation between the inhibitor approach and the stabilizer approach was surprisingly good. Some boronic acids with large organic moieties had very limited solubility and since the modeling studies had suggested that these compounds were not expected to be strong inhibitors they were rejected without further attempts to solve the solubility issues.

5.5.1 Enzyme Kinetics and Determination of K_i in a Buffer System

When an enzyme is mixed with a large excess of substrate (which is generally the case due to the high catalytic efficiency of enzymes), there is an initial period, the pre-steady state period, during which the concentrations of enzyme bound intermediates build up to their steady state levels. Once the intermediates reach their steady state concentrations (and this is generally achieved after milliseconds) the reaction rate changes only slowly with time.

It is during this steady state period that the rates of enzymatic reactions are traditionally measured and the parameter measured is the initial rate v of product formation – that is the formation of the first few percent of the products so that the substrate is not depleted and the products(s) have not yet accumulated.

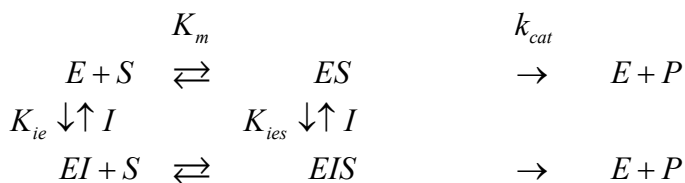
It has been found experimentally that in most cases v is directly proportional to the concentration of enzyme $[E_0]$ and that v generally follows saturation kinetics with respect to the concentration of substrate $[S]$: At low $[S]$ v increases linearly with $[S]$, but as $[S]$ increases v increases less rapidly than $[S]$ until v approaches a limiting value called V_{max} . This is expressed quantitatively in the Michaelis-Menten equation originally proposed by Michaelis and Menten. K_m can be seen as an apparent dissociation constant for the enzyme-substrate complex ES . The maximal velocity $V_{max} = k_{cat} [E_0]$.

$$v = k_{cat} \frac{[E_0][S]}{K_m + [S]}$$

The Michaelis-Menten equation can also be derived by applying the steady state assumption to the following scheme:



The boronic acids are assumed to inhibit the proteases according to the reaction scheme below



The kinetic parameters k_{cat} and K_m were determined without inhibitor and at several inhibitor concentrations. The inhibition constants K_{ie} and K_{ies} were calculated from plots of K_m/k_{cat} and $1/k_{cat}$ as a function of the concentration of inhibitor.

The substrate used was the synthetic peptide N-Succinyl-Alanine-Alanine-Proline-Phenylalanine p-Nitroanilide which upon hydrolysis liberates 4-Nitroaniline which is conveniently measured at 410 nm.

The inhibition constants found for the more promising inhibitors were typically below $K_i = 10^{-4}$ M, that is several orders of magnitude lower than the inhibition constant for boric acid as expected.

In conclusion, this approach was more or less a characterization method adopted from a biochemistry (enzyme kinetics) textbook.

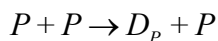
5.5.2 Storage Stability Trials in Model Liquid Detergent

A model liquid detergent was developed to have a well-known base to evaluate the inhibitor candidates. The detergent was chosen to give a fast response, i.e. a detergent with relatively poor enzyme stability. The storage time for a good response was less than three weeks. The inhibitor candidate was dissolved in the detergent and both a protease and a lipase (protease labile enzyme) were added to the detergent. The detergent was allowed to equilibrate for some hours before storage at 35°C in closed glasses. The protease and lipase activities were measured with standard assays before and after storage. As references, detergent without inhibitor, detergent with boric acid inhibitor and detergent with only the lipase were used.

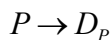
To calculate the efficiency of the candidate inhibitor from the storage stability data, it is necessary to propose a reaction mechanism. The following set of

reactions give a very simple but yet plausible mechanism for a liquid detergent containing a protease (P), a lipase (L) and an inhibitor (I):

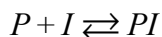
I) Autodigestion of protease:



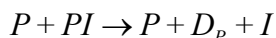
II) Denaturation of protease:



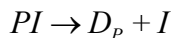
III) Inhibition of protease:



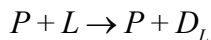
IV) Protease digestion of inhibited enzyme:



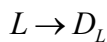
V) Denaturation of inhibited enzyme:



VI) Protease digestion of lipase:



VII) Denaturation of lipase:



Where D_X is a general term for denatured protein X of all kinds. The inhibitor (and all other non-enzymatic components in the detergent) was assumed to be stable in the detergent, i.e. no inactivation of the inhibitor occurs. Reaction III is expected to be much faster than the other reactions and equilibrium is assumed in the calculations. Reaction IV was excluded from the system to reduce the

number of parameters, thus describing the stability of the inhibited enzyme by a single parameter only.

From the resulting reactions a set of coupled differential equations can be derived describing the deactivation of P, L and PI and the reaction rate constants can be derived from storage stability data by the use of parameter estimation methods. The storage stability data give the concentration of P+PI (it is assumed that the inhibitor fully releases the protease during analysis due to fast dynamics and the extensive dilution in the assay) and L as a function of time.

The specific values of the reaction rates are somewhat sensitive to variations in the data (day-to-day variations in the analysis, batch-to-batch variations of the model detergent etc.), but the sensitivity is reduced significantly by expressing the results relatively to the values obtained from boric acid tested in the same experiment. An improvement factor IF_I is derived:

$$IF_I = \frac{K_I \text{ (Boric Acid)}}{K_I \text{ (Inhibitor)}}$$

IF_I measures the inhibition efficiency given by the inhibition constants K_I from reaction III.

The stability of the inhibited protease (reaction V) is also important. For most of the inhibitors tested this was relatively close to that of Boric acid. The measured Improvement Factors (IF_I) from a selected set of experiments are listed in Table 1.

Table 1: Measured Improvement Factors for a selected set of Inhibitors

Inhibitor	IF_I
Boric acid	1
2-Formylphenyl boronic acid	36
3-Formylphenyl boronic acid	230
4-Formylphenyl boronic acid	1000
Acetamidophenyl boronic acid	300
4-Carboxyphenyl boronic acid	22
Naphtalene-1 boronic acid	5
Naphtalene-2 boronic acid	30
6-Hydroxynaphtalene-2 boronic acid	26

5.6 CONCLUSIONS

The most promising candidate after testing more than 50 inhibitors was 4-formylphenyl boronic acid (4-FPBA). This candidate (along with a few others included for comparison) was tested for efficiency in several detergents including commercial types with good results. Figure 3 shows the typical efficiency of 4-FPBA in liquid detergent containing lipase and protease. In this case the efficiency is around 100 times that of boric acid. This and other promising candidates were patented (Nielsen & Deane-Wray, 2000, 2002)

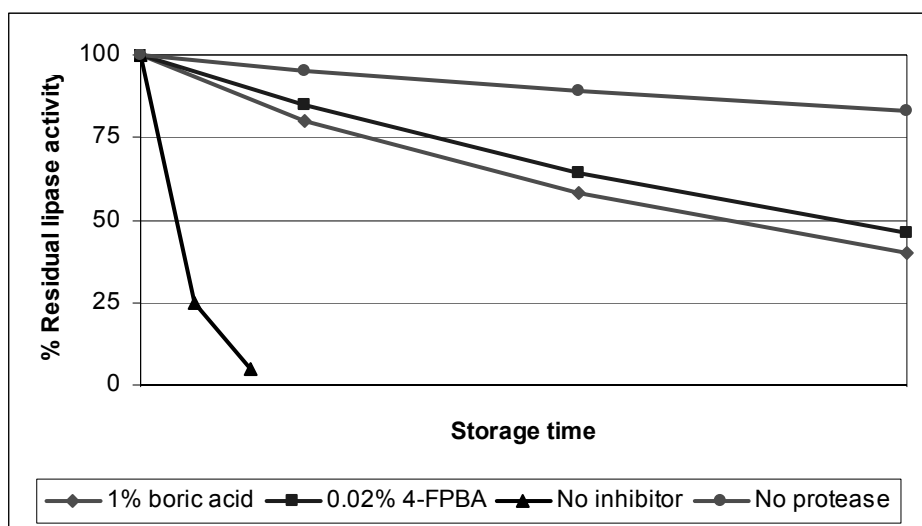


Figure 3: Typical efficiency of 4-FPBA in liquid detergent containing lipase and protease. In this case the efficiency is around 100 times that of boric acid

At this stage of the project, the opportunity arose to have a handful of the boronic acids crystallized together with subtilisins and to get the three dimensional structure determined by means of X-ray crystallography. This was done in collaboration with Institut de Biologie Structurale in Grenoble (Verger, 1996). To our pleasant surprise we found that the correlation between “the inhibitor approach” and “the stabilizer approach” was extended to the “the X-ray crystallographic approach”. So the X-ray crystallographic studies may not have provided us with new information, but they did indeed suggest that we were on the right track.

Wash performance trials were performed to verify that the enzyme was liberated from the enzyme inhibitor complex in the wash and the expected washing performance could indeed be achieved. A range of toxicology studies were also conducted and they did not suggest that toxicological issues would be a show stopper especially when it was taken into account that the boronic acid was to be used in very low concentrations.

The development work inclusive toxicology studies proceeded smoothly and took some years. The most time consuming part of the development turned out to be identification and development of a feasible and economical way to synthesize the compound. The complexity of this issue was initially underestimated. One thing is defining a route of synthesis and producing a small amount of inhibitor in a laboratory environment. Taking a process to industrial scale production, where e.g. availability of bulk quantities of a start material and handling of organic solvents become very important factors is a completely different set-up which turned out to be more complicated and time consuming than first expected.

The final development of the enzyme product after identification of the inhibitor and establishment of an industrial production process turned out relatively easy after initial solubility issues were solved.

There are now several products on the market including the inhibitor (Biotimes, 2002). Reviewing the decade that passed from the initial idea to commercial product one may argue that there should have been focus on the industrial scale production of the boronic acids from the early phases of the project already. Had we however, put too many constraints on ourselves in the early phases of the project we may never have reached the goal.

REFERENCES

- Biotimes. Visit the home page www.biotimes.com, June 2002
Boskamp, J.V. (1982), US patent 4,462,922
Hiromi, K; Akasaka, K; Mitsui, Y; Tonomura, B & Murao, S (eds) (1985)
Protein Protease Inhibitor – The Case of Streptomyces Subtilisin Inhibitor.
Elsevier Amsterdam – Oxford – New York.
Jonassen, I (1980) Characteristics of Hiproly Barley I. Isolation and
Characterisation of two Water-Soluble High-Lysine Protein *Carlsberg Res. Commun.* **45**, 47-58
Kraut, J. (1977) Serine Proteases: Structure and Mechanism of Catalysis: *Ann. Rev. Biochem* **46** 331-358

- Lai, K. Y. (Ed) (1997), *Liquid Detergents*, Surfactant Science Series, Vol. 67, Marcel Dekker, New York
- Laskowski, M & Kato, I (1980) Protein Inhibitors of Proteinases. Ann. Rev. Biochem. **49**, 593-626.
- Lindquist, R. N. & Terry, C (1974). Inhibition of Subtilisin by Boronic Acids, Potential Analogs of Tetrahedral Reaction Intermediates, Arch. Biochem. Biophys. **160**, 135-144.
- Matthews, D.A.; Alden, R.A; Birktoft, J.J.; Freer, S.T.& Kraut, J (1975) X-ray Crystallographic Study of Boronic Acid Adducts with Subtilisin BPN' (Novo). J. Biol. Chem. **250**, 7120-7126.
- McPhalen, C. A. & James, M. N. G (1988) Structural Comparison of Two Serine Proteinase-Protein Inhibitor Complexes: Eglin C- Subtilisin Carlsberg and CI-2 Subtilisin Novo) Biochem. **27**, 6582-6598.
- Ness, J. Simonsen, O. & Symes, K (2003) Microcapsules for Household Products. Arshady, R. & Boh, B. (eds) Microcapsule patents and products, MML series vol. 6, Citus Books.
- Nielsen, L.K. & Deane-Wray, A (2000), EP 0 793 709 B1
- Nielsen, L.K. & Deane-Wray, A (2002), EP 0 832 174 B1
- Polgar, L. (1987) Structure and Function of Serine Proteases in Hydrolytic Enzymes, Neuberger & Brocklehurst (eds.) Elsevier Science Publishers B.V. (Biomedical Division) 159-200.
- Tai, H.T. (1982), US patent 4,404,115
- van Ey, J.H. Misset, O. & Baas, E.J. (Eds) (1997), *Enzymes in Detergency*, Surfactant Science Series, Vol. 69, Marcel Dekker.
- Verge, D (1996). Ph.D thesis on the X-ray crystallographic studies of Subtilisins in complex with boronic acids.
- Von der Osten, C. Hedegaard, L; Østergaard, P, Lauridsen, C, Kierstein, L & Branner, S. (1993) "Stabilization of the detergent protease Savinase by proline substitution" in "Stability and Stabilization of Enzymes", Van den Tweel, W.J.J., Harder, A & Buitelaar, R.M. (eds), Elsevier Science B.V., The Netherlands.

Chapter 6

Process Synthesis for structured food products

F. Michiel Meeuse

Unilever Food and Health Research Institute, Olivier van Noortlaan 120, 3133 AT Vlaardingen, The Netherlands

6.1 INTRODUCTION

A typical characteristic of many food products is that these are multi-phase products. The arrangement of the different phases leads to a microstructure that determines the properties of the product. Mayonnaise, for example, is an emulsion of about 80% oil in water, stabilized by egg yolk protein. The size of the oil droplets determines the rheology of the mayonnaise, and hence, the mouthfeel and the consumer liking. Ice cream is a product that consists of four phases. Figure 1 shows this structure schematically. Air bubbles are dispersed in a water matrix containing sugar molecules and ice crystals. The air bubbles are stabilized by partial coalesced fat droplets. The mouthfeel of ice cream is determined by a combination of the air bubble size, the fat droplet size and the ice crystal size.

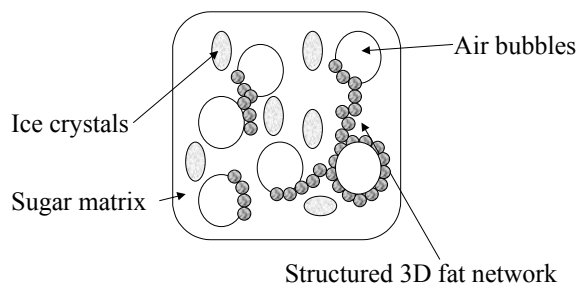


Figure 1. Structure of ice cream

Traditionally, the processes for these type of food products were designed in an evolutionary way. Sometimes the process is just a large scale kitchen. Although

these designs did lead to acceptable products, there is a need for a much more systematic design of such processes. The two main drivers for this are the need for more cost effective designs and the need for a high innovation rate. Being first on the market with new innovations becomes more and more critical and this can only be guaranteed when the process design is addressed systematically.

In the last decades a lot of developments took place in the field of systematic methods for designing chemical processes. A lot of examples are published where breakthroughs have been achieved by not looking at a process as a combination of unit operations, but by understanding the fundamental phenomena happening in the process. Most applications of process synthesis were, however, demonstrated for traditional chemical product processes. Extending these methods to structured food product processes is not straightforward, given the following clear differences between these products:

- The performance of the product is not only determined by its chemical composition and its purity, but also by the product micro structure.
- The unit operations involved are quite different, less reaction and separation, more mixing, crystallization and preservation.
- Food processes are generally multi product processes – so, on the same production line, different products with different properties need to be produced.
- Cleaning is an essential part of the operational policy for food safety and product quality reasons.

Initial work on the design of structured products has been presented by, for example, Meeuse et al. 2000, Wibowo and Ng, 2001, 2002. In this chapter a real life example of a process redesign project where process synthesis techniques were applied to a structured food product, is presented. First, we position this work in the framework of integrated product and process design. Then we describe how we translated existing process synthesis techniques into a useful methodology for structured products. Then the actual case study is presented. Finally some perspectives are given.

6.2 PROCESS DESIGN VS. PRODUCT DESIGN

In the open literature, various ideas are presented on the relation between process design and product design. Cussler and Moggridge (2001) have presented a four-stage product design methodology where the manufacturing of the product is only considered after the selection of the product, that is, once the product design is finished. The risk of the strict sequential approach is that a product developer might come up with a product that fulfils the needs very well

but is very difficult or expensive to produce. Hostrup et al. (1999), and, Linke and Kokossis (2002) have presented examples where the design of a solvent and the separation process were carried out simultaneously using hybrid optimization-based approaches. Such a simultaneous approach for product and process design is typically not possible for structured food products since rigorous models describing all relevant phenomena are typically not available.

Wei (2004) and Hill (2004) show that the industrial reality is somewhere in between these two extreme approaches. Ideally, process engineering is already considered in the very first stages of the product design. In these stages the process engineering involvement will be rather limited, although, it will be increasing over the next stages of the product design process. Within Unilever, process engineers are usually involved in product development activities. They give processing input in the product development project. This is important since small differences in the product design can have a huge effect on the process design. However, this does not mean that product design and process design are fully integrated. They are still two sequential activities but during the product design, some of the processing issues are considered explicitly.

The importance of considering the processing already from an early point in time is demonstrated by the following examples.

6.2.1 Example 1

A completely new sauce like product was developed. The developed product contained small chunks of a specific, soft vegetable. This product made on the laboratory scale scored well in various tests. However, scaling up was very hard given the soft character of the vegetable pieces. The high shear rates in various parts of the processes (including the generally neglected filling machines) completely mashed the chunks. An alternative product without the chunks was much easier to produce. This alternative product also scored well with consumers, but significant time was lost before this was realized. Earlier involvement of processing considerations would probably have led to the same end result, but in a shorter time frame.

6.2.2 Example 2

An emulsified product was developed that contained both fat with a melting point of about 40°C and oil. As a result the emulsification cannot take place at ambient temperatures, it should take place at temperatures above 40°C. The consequence was that the product could not be made in the equipment currently available in the factory. When the product was modified, the fat was replaced

by liquid oil, the consumer liking remained the same. However, significantly reduced investment was required since the already available equipment could be used.

In the rest of this chapter attention will be on the process design issues and it will be assumed that the product specifications are already given.

6.3 PROCESS SYNTHESIS METHODOLOGY

In the field of process synthesis, there are basically three different approaches available: (1) mathematical optimization based approaches, (2) heuristic based approaches, and (3) hybrid approaches

In the mathematical optimization based approaches first a superstructure is created which has embedded a large number of alternative designs. Then mathematical techniques like MINLP are used to find the optimum process within the specified superstructure. For the products considered here there are two big hurdles preventing the large scale use of these techniques (Hill, 2004). Firstly a lot of the physico-chemical phenomena occurring are not completely understood. This makes rigorous modeling difficult. Secondly there is a lack of relevant property models for structured products.

Heuristic based approaches are more relevant for structured products. The most well known heuristic based approach is the hierarchical decomposition method developed by Douglas (Douglas, 1988). In the first level of this method one only looks at the input-output structure of the process. In subsequent levels more detail is added, finally ending with the entire flowsheet. Design decisions are made by using heuristics and short-cut models. An alternative method is due to Siirola (1996); means end analysis. In this method the properties of the feedstock and the desired products are compared. Tasks are defined to eliminate the property differences between the feedstock and the desired product.

The hybrid approach tries to combine the model-based optimization approach with the heuristic approach, thereby, avoiding the problems of unavailability of models. In the initial stages, a property-based approach (where properties are obtained through model or experimental measurements) is applied and in the final stages (where models are usually easy to develop), a model-based optimization approach is applied (see for example, Gani (2004)). More work is needed to establish this technique for food-process applications.

The method we are using is a combination of the hierarchical decomposition (Douglas, 1988) and means end analysis (Siirola, 1996). The three first stages of

the hierarchical decomposition are input/output structure, task blocks and unit operations.

6.3.1 *Input/output Structure*

In this level we specify the input (raw material) and the output (products) of the process. In this chapter, we will focus on single product processes only, but the method is not limited to this. The specification of the outputs includes a specification of the microstructure of the products, as well as other parameters, such as, the flavor profile and the microbiological status of the product. For the product microstructure one should specify the composition of the various phases of the product how the phases are arranged, and the interfacial composition. So for an emulsion one needs to specify:

- The composition of the continuous phase
- The composition of the dispersed phase
- The size distribution of the dispersed phase
- The interfacial composition

For the microbiological status, there are specifications that the microbiological composition is less than a certain limit and that no pathogenic microorganisms are present. These limits will depend on the product characteristics (e.g. pH, salt level) and storage temperature and shelf life. However, for certain products (e.g. yogurt) there are also specifications that the product should contain a minimum level of specified microorganisms.

6.3.2 *Task Identification*

In this level, the fundamental tasks required to convert the raw materials into the final product are identified. All tasks are related to property differences. Siirola (1996) has presented the following hierarchy of property differences: molecular identity, amount, composition, phase, temperature/pressure, form. This list of tasks is not very well suited for food properties. Common tasks for food processes are decontamination (e.g. pasteurization and sterilization) and structure formation (e.g. emulsification, size reduction of dispersed phase in an emulsion, crystallization, interfacial adsorption/desorption).

It is not trivial to put these tasks in a hierarchy. Therefore, the proposed way of working is to identify the tasks first and then, based on insights, decide the order in which these tasks need to be resolved. This can be an iterative process between this stage and the next stage, unit operations.

6.3.3 Unit Operations

The next step is to transform these tasks into unit operations. This does not mean that there is a one to one relation between a task and a unit operation. Often, various tasks can be carried out in a single unit operation. The operating conditions of these unit operations should be designed such that the tasks are fulfilled. Similar to the method proposed by Douglas (1988), short-cut process and physical property models and heuristics are used for the decision making. For instance, assuming that for an identified task of droplet size reduction, the diameter of droplets of an emulsion should be about 8 μm . For the selection of the emulsification devices, heuristics can be applied, leading to the selection of a colloid mill. The model presented by Wieringa et al (1996) can then be used to design the colloid mill.

6.4 EXAMPLE

Consider the following real life example of a process for a specific product “P”. This product is an oil-in-water emulsion with a droplet size of about 2 μm . The emulsion is stabilized by two different emulsifiers, “E1” and “E2”. E1 is a so-called small emulsifier and E2 a so-called big emulsifier. The product developer specifies the levels of the oil, E1 and E2 and the water phase.

There is already an existing process for this product. This process is shown schematically in Figure 2. It consists of the following processing steps:

- mixing of all ingredients
- homogenization
- pasteurization
- cooling
- maturation

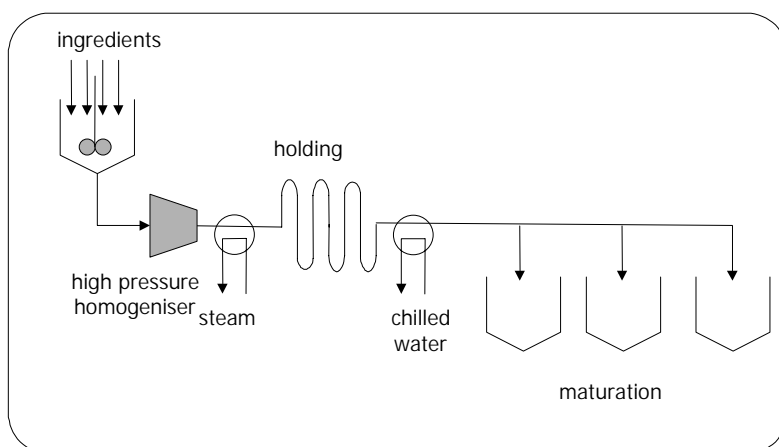


Figure 2. Process flow diagram

The maturation step was considered to be the bottleneck of the process. The residence time in this process takes up to 6 hours, limiting the flexibility of the plant. Moreover, one should realize that this process step takes place after the pasteurization step. Hence the hygienic requirements for this process step are quite strict and the capital costs for this part is high. We wanted to do a redesign of this process, leading to the same product, but ideally without the maturation step. This was done by applying the process synthesis techniques discussed above.

6.4.1 Input/output Structure

The product microstructure is specified as follows. The product is an oil in water emulsion. The oil droplet size should be around $2\mu\text{m}$. The emulsion is stabilized by two different emulsifiers, E1 and E2. Both emulsifiers should be at the interface in a certain ratio. Since there is an excess level of E1, the remaining E1 should be dispersed in the water phase. The levels of the oil, E1 and E2 and the water phase are specified. The microstructure is shown schematically in Figure 3.

Since the product formulation would allow growth of vegetative microorganisms that would be in the product, the microbiological status of the product is specified as follows: "In the product no living vegetative microorganisms are allowed."

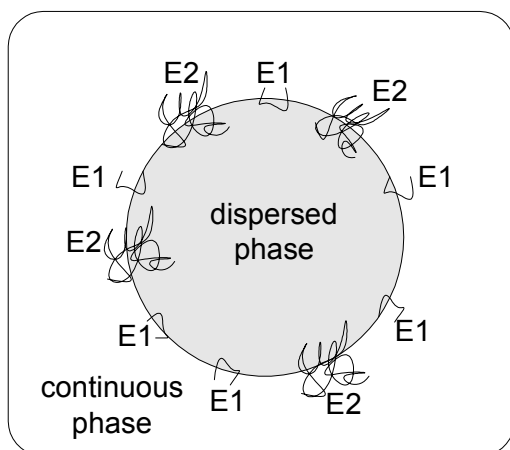


Figure 3. Schematic representation of product microstructure.

6.4.2 Tasks Identification

One way to identify the tasks needed to go from the raw materials to the end product, is to look at the tasks of the current process. For some process step the associated tasks are quite clear. For example, the tasks associated with the process step *mixing of ingredients* are *dispersing the oil in the water phase* and *dissolving all powder ingredients*. However, the tasks associated with the maturation step requires a fundamental understanding of physico-chemical phenomena occurring in the process. We found out that the true task of this step was to obtain the required interfacial composition. This was revealed by studying data on the interfacial tension at the water/oil interface, as a function of the temperature for emulsions with only E2 and with both E1 and E2. This data indicated that:

- At temperatures above 10°C, the interfacial tension of both emulsions is about 10 mN/m.
- At temperatures below 10°C, the interfacial tension of the emulsion with only E2 is about 10mN/m, but the interfacial tension of the emulsion with both E1 and E2 is reduced to about 3 to 5 mN/m.

Based on the above observations, one can conclude that at temperatures below about 10°C, the thermodynamic optimum structure is the target structure: a combination of both emulsifiers adsorbed at the surface. At higher temperatures, however, there is no clear thermodynamic difference between an emulsion where the surface is covered with E1 only or an emulsion where the surface is covered by a combination of E1 and E2. Since E1 is available in excess

quantities, the surface after homogenization is mainly covered with E1. So in the maturation process the surface composition is reconfigured; part of E1 is replaced at the interface by E2. This is a thermodynamically driven process.

Table 1 shows the tasks associated with the processing steps of the current process as shown in Figure 2.

Table 1 Existing process steps with the corresponding tasks.

Process step	Task
mixing of ingredients	Dispersing the oil in the water phase Dissolving all powder ingredients
homogenization	Size reduction of the oil droplets
pasteurization	Killing all vegetative microorganisms
cooling	Temperature reduction
maturation	Reconfiguration of interfacial composition

Both the *temperature reduction* tasks and the *reconfiguration of interfacial composition* task are not fundamentally required. The temperature reduction is required since the pasteurization tasks leave the product at too high a temperature. The interfacial reconfiguration is required since the interfacial configuration after the cooling step is not the desired one.

6.4.3 Unit Operations

Based on the identified fundamental tasks given in Table 1, an alternative process was developed without the need for a maturation step. The basic idea was to add only a limited amount of E1 in the *mixing of ingredients* step. The hypothesis was that the results should be such that the interfacial composition after homogenization was already the finally desired one since no excess of E1 would be present. The remaining E1 would then be post-dosed, only after the pasteurization phase.

The first step to verify the feasibility of this was to do experiments to see if the level of emulsifier E1 has an effect on the droplet size obtained during the emulsification. Figure 4 shows the effect of the level of E1 added to the premix vessel on the average droplet size of the emulsion after homogenization. The relative droplet size shown in Figure 4 are relative to the droplet size obtained in the reference (100% E1). Figure 4 clearly shows that up to about 25% E1 there

is a reduction of droplet size with increasing level of E1. But in the range from 25% to 100% the droplet size is independent of the level of E1 in the premix. So this gives the opportunity to post-dose up to 75% of E1 without an effect on the droplet size after homogenization.

Based on this result the alternative process was designed based on the post-dosing of part of E1. The process is shown schematically in Figure 5. Compared to the current process the only differences are that there is no maturation step and that part of E1 is post-dosed.

All unit operations were designed with similar models and guidelines as used for the current process. Different types of models and guidelines are available for the different unit operations.

Sizing of the tank for the mixing of ingredients is done with very basic engineering methods. The required mixing times are determined based on experimental data of existing processes.

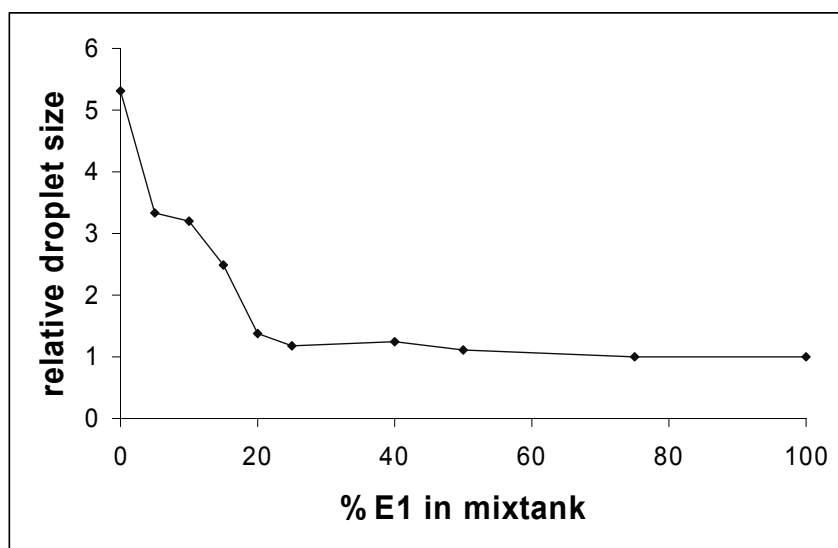


Figure 4. Effect of level E1 in mixing tank of the droplet size

In the heating and cooling steps, the structure of the product does not really lead to a different behavior compared to a homogeneous liquid. So when the relevant physical properties are known (viscosity, heat capacity, thermal conductivity,

density), conventional first principles based models can be applied for the design of these step. The needed physical properties are typically obtained through experimental measurements.

Various models are available that describe the droplet size obtained through emulsification devices as a function of the operating conditions. Wieringa et al. (1996) present a model specific for emulsification in a colloid mill. Karbstein and Schubert (1995) present the following relation between the energy of dissipation and the mean droplet diameter, applicable for a range of emulsification devices, including a high pressure homogenizer:

$$d_{32} = a \cdot E_v^{-b}$$

where d_{32} is the Sauter mean diameter, E_v is the volumetric energy dissipation rate and a and b are constants. Such models give a good indication of the trends but in order to design equipment we need to know the values of the constants. Therefore, experimental information is used to assist in the design of such pieces of equipment.

6.4.4 Evaluation

Some experiments have been conducted to verify the feasibility of the process shown in Figure 5 on pilot plant scale. With the correct level of E1 post-dosed, a similar product microstructure could be obtained. And more importantly, the physico-chemical and sensory properties of the product produced with the new process were found to be similar to the product properties from the original process.

An economic evaluation of this alternative process showed that for a grass roots design, the capital costs of the new process would be reduced by about 25%, compared to the current process.

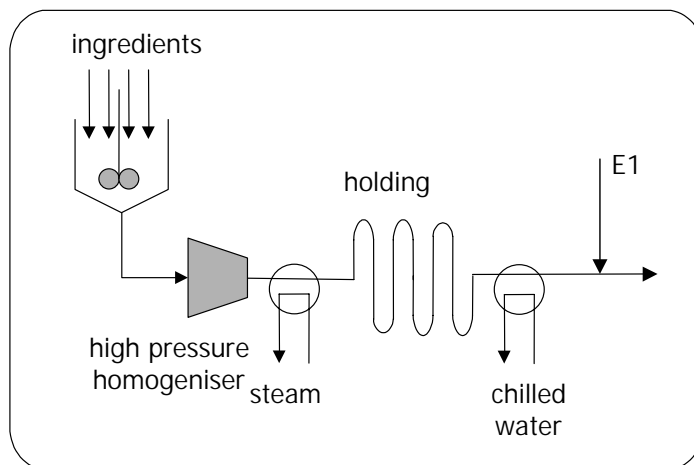


Figure 5. Schematic overview of alternative process

6.5 RESEARCH CHALLENGES

The example presented in section 6.4 of this chapter showed that process synthesis can be applied to structured food products. Moreover this application is of true value since significant cost savings could be achieved. However, a complete methodology is not yet available. One of the main outstanding questions is how to perform the identified (necessary) tasks in an optimal sequence to obtain the desired product? Besides this the success of application depends critically on the availability of domain knowledge about all relevant aspects of the process. Several factors relevant for food processing were not considered in this example:

- The example presented was aimed at a single product process. Multi-product processes will increase the complexity of the problem. Especially when the different products also have different microstructures. Scheduling could become an essential aspect of the design process.
- The quality of the final product is partly determined by the hygiene/cleaning systems in the factory. So aspects such as modeling of microbiological growth, decontamination, soil removal and the hygiene level in the process become essential.

Further developments in these areas will certainly lead to increased application of process synthesis methods and tools within the food industry.

REFERENCES

- Cussler and Moggridge, 2001, Chemical product design, Cambridge University Press.
- Douglas, J., 1988 Conceptual process design, McGraw-Hill.
- Gani, R. Chemical product design: Challenges and opportunities, Computers and Chemical Engineering, 28(2004) 2441-2457.
- Hill, M., 2004 Product and process design for structured products, AIChE Journal 50, 1656 – 1661.
- Hostrup, M., Harper, P. M., Gani, R., 1999, Design of environmentally benign processes: Integration of solvent design and separation process synthesis, Computers and Chemical Engineering, 23(1999) 1395-1414.
- Karbstein, H. and Schubert, H., 1995, Developments in the continuous mechanical production of oil-in-water macro-emulsions, Chemical engineering and processing, 34, 3, 205 – 211.
- Linke, P. and Kokossis, A., 2002, Simultaneous synthesis and design of novel chemicals and chemical process flowsheets, Computer Aided Chemical Engineering, 10, 115.
- Meeuse, F.M., Grievink, J., Verheijen, P.J.T. and Stappen, M.L.M. vander, 2000, Conceptual design of processes for structured products, in: Malone, Trainham and Caranhan (eds) Fifth international conference on Foundations of Computer Aided Process Design, 324 – 328.
- Sirola, J., 1996 Industrial application of chemical process synthesis, Advance in Chemical Engineering, 23, 1 – 92.
- Wei, J., 2004 The integration of process and product design, Proceedings of FOCAPD 2004.
- Wibowo, C. and Ng, K.M., 2001 Product oriented process synthesis and development: creams and pastes, AIChE Journal, 47, 2746 – 2767
- Wibowo, C. and Ng, K.M., 2002 Product centred processing: manufacture of chemical-base consumer products.
- Wieringa, J.A.; Dieren, F. van; Janssen, J.J.M.; Agterof, W.G.M., 1996, Droplet breakup mechanisms during emulsification in colloid mills at high dispersed phase volume fraction, Chemical Engineering Research & Design, 74, 554-562.

Chapter 7

Marine biofouling protection: design of controlled release antifouling paints

Søren Kiil,^a Claus E. Weinell,^b Diego M. Yebra,^b Kim Dam-Johansen^a

^a*Department of Chemical Engineering, Technical University of Denmark, Building 229, DK-2800 Kgs. Lyngby, Denmark*

^b*Hempel A/S, Lundtoftevej 150, DK-2800 Kgs. Lyngby, Denmark*

7.1 Introduction

This chapter is concerned with the design and improvement of chemically-active ship bottom paints known as antifouling paints. The aims have been to illustrate the challenges involved in working with such multi-component, functional products and to show which scientific and engineering tools are available. The research in this field includes both purely empirical formulation and test methods and advanced tools including mathematical modelling of paint behaviour.

First, the background of and problems associated with marine biofouling are presented. This is followed by a concise historical review showing the diverse ideas of biofouling control that have been tried over the years. The next section deals with the characterisation and working mechanisms of antifouling paints, detailing the various components and their function. Practical laboratory and field tests of antifouling paints are subsequently discussed. Then follows a section on mathematical modelling of antifouling paint behaviour illustrating how such quantitative tools can be used in the design and understanding of new and improved paint systems. The final issue raised is the approval of paint products, which is of great importance because antifouling paints contain active

ingredients. The chapter ends with conclusions and a look ahead for new solutions to the marine biofouling challenge.

7.2 Marine Biofouling

7.2.1 Characterization of Marine Biofouling

Marine biofouling can be defined as the undesirable colonisation of man-made structures immersed in sea water by biotic and abiotic dissolved compounds, microorganisms, plants and animals (see Fig. 1, Rittschof, 2001; Bertram, 2000; Yebra *et al.*, 2004).



Figure 1: Removal of biofouling from a ship. Hempel A/S.

Seconds after immersion (Bertram, 2000), the biofouling process will commence with the physical adsorption of dissolved organic matter such as polysaccharides and proteins at the submerged surface (i.e. a ship hull), giving rise to the so-called conditioning film (Abarzua and Jabubowski, 1995; Yebra *et al.*, 2004). Marine organisms will also tend to attach to such a surface, where they can make use of the natural movement of the sea water for feeding and waste removal, thus saving energy for other vital processes (Rittschof, 2001). Despite these energetically advantageous conditions, the number of sessile species which can tolerate the wide fluctuations in environmental conditions as those experienced by e.g. a seagoing ship hull is relatively small (about 4,000; Anderson and Hunter, 2000) compared to the vast amount of known marine species (Yebra *et al.*, 2004).

There are countless numbers of different attachment cues and attachment mechanisms used by marine foulers to colonize a surface, which makes any attempt of generalizing rather futile (Rittschof, 2001). The most classical description of the fouling process is based on the *successional fouling* hypothesis (Rittschof, 2001; Bertram, 2000; Yebra *et al.*, 2004), which is based on the assumption that the settlement of macrofoulers is dependant upon prior colonization by inferior fouling species (Rittschof, 2001). According to this theory, once the conditioning film is stabilised, rapidly developing bacteria and single-cell diatoms attach to the surface by secreting large amounts of mucilaginous extracellular polymeric substances (EPS) to form biofilm structures or “slimes” (Bertram, 2000; Anderson *et al.*, 2003; Yebra *et al.*, 2004). Algal spores, barnacle cyprids, marine fungi and protozoa detect the surface, most likely attracted by sensory stimuli, and subsequently adhere to it (Bertram, 2000; Yebra *et al.*, 2004). The final stage would consist on the settlement and growth of larger marine invertebrates and macroalgae (Figure 2). The hypothesis of a *successional fouling* sequence implies that the blocking of one of the early stages would hinder the progress of the subsequent stages (Clare *et al.*, 1992; Rittschof, 2001; Yebra *et al.*, 2004). Unfortunately, organisms such as barnacles are attracted by high surface energy, unfouled surfaces and many hydroids settle on any surface independently of their fouling history (Rittschof, 2001). For those organisms, a *probability-driven* theory for fouling (depending on a probability of contact and a subsequent probability of settlement) is more suitable (Rittschof, 2001).

The local severity of fouling mainly depends upon the sea water temperature, which determines the breeding periods and growth rates of marine foulers, salinity and the amount of solar radiation (WHOI, 1952). Coastal waters, rich in nutrients, pose a higher fouling risk than open ocean waters, while fouling species are much less plentiful in the dark deep waters compared to the sea surface (Yebra *et al.*, 2004). Despite these regional patterns, several fouling species have succeeded in colonizing the harbours all over the globe thanks to short-lived microscopic larvae, spores, or propagules that settle, metamorphose, and complete their life cycle in less than a month and stay reproductive much of the year (Rittschof, 2001). The copper-resistant green algae *Ulva* spp. (formerly *Enteromorpha* spp.) and barnacles such as *Balanus amphitrite* are amongst the most ubiquitous fouling species (Rittschof, 2001) and their settlement on ship hulls is associated with severe economical and environmental penalties.

then been removed. It appears that this barnacle adhered very strongly to the painted surface since most of the paint system under the barnacle was pulled off and remained on the barnacle basal edge.



Figure 3: Tropical barnacle with paint remains adhering to the base. To the left: side view, to the right: top view. Size is seen relative to a pen.

Of environmental concern is the introduction of species into environments where they were not naturally present (invasive species) due to long range transportation of water in ballast tanks. Vessels immersed can allow fouling communities to develop and spread beyond their native distribution which in some cases will have unwanted consequences for the environment, economics and human health (Minchin and Gollasch, 2003; Godwinn, 2003).

7.3 Historical Aspects of Antifouling

Being a natural and ubiquitous process, the problem of marine fouling has troubled mankind since the very birth of navigation (Figure 4). Written testimonies of early antifouling (AF) attempts are available from ancient Mediterranean civilizations such as Phoenicians, Carthaginians, Greeks and Romans (WHOI, 1952). Such early solutions, not really successful, relied on e.g. arsenic, sulphur and oil mixed with pitch, wax, tar or asphaltum (WHOI, 1952). Pitch, occasionally blended with resin, oil, and tallow, was very common from the 13th to the 15th centuries, being used in e.g. Christopher Columbus' expedition to the New World (WHOI, 1952). Nevertheless, and despite its deficient performance (barely efficient against tubeworms), the most

widespread AF system until the 18th century was lead sheathing (WHOI, 1952). In 1758, the use of copper sheathing on the *HMS Alarm* yielded improved results compared to lead sheathing, and soon became the preferred technology to protect the hulls of wooden ships (WHOI, 1952). The advent of steel ships and the subsequent corrosion problems associated with metallic sheathing precipitated the abandonment of such a technology and left room for the development of AF paints (WHOI, 1952).

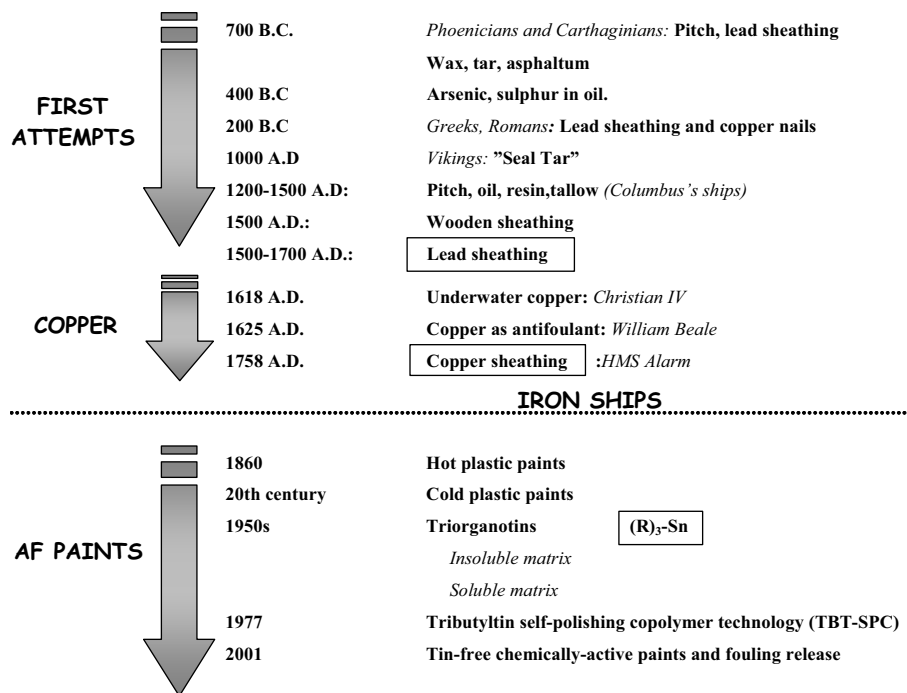


Figure 4: Historical development of antifouling methods.

In 1625, William Beale patented the first AF paint, which consisted of powdered iron and a copper compound dispersed in cement (WHOI, 1952). During the mid 1800s, William John Hay's idea of isolating the iron hull from the metallic toxicants using a non-conductive varnish gave rise to many AF paints using e.g. copper oxide, mercury oxide and arsenic dispersed in a variety of resins (WHOI, 1952). Following the research carried out in the early 20th century by the US Navy, rosin demonstrated advantageous properties as a carrier system, especially when combined with the synthetic, petroleum-derived resins which appeared after World War II (Yebra *et al.*, 2004). In the mid 1950s, the incorporation of the highly toxic, broad-spectrum organotin

compounds into AF paints markedly improved their performance. Up to 1974, tributyltin(TBT)-compounds such as the bis-oxide (TBTO) and the fluoride (TBTF) were dispersed into the AF matrix, i.e. in “free-associated form”. Some years later, the patent of Milne and Hails regarding the development of an AF binder composition consisting of an acrylic resin to which TBT groups were chemically linked, revolutionised the AF paint industry (Yebra *et al.*, 2004).

This invention, which was given the commercial name of tributyltin self-polishing copolymer technology (TBT-SPC), managed to overcome the fast leaching of the TBT-bearing compounds when incorporated in free-associated form, thus yielding long-lasting AF protection (Omae, 2003; Yebra *et al.*, 2004). Overall, the main advantages of TBT-SPC can be summarised as (see working mechanisms in a later section):

- Smooth paint surfaces during sailing (i.e. good hydrodynamic profile and reduced fuel consumption)
- Sufficient and virtually constant biocide release rates over time even during stationary periods

The success of this technology propitiated that more than 70% of the world fleet of ocean-going ships had their hull painted with TBT-SPCs during the 1990s (Yebra *et al.*, 2004). Unfortunately, it was soon realised that TBT-bearing biocides do not degrade sufficiently fast in the sea water column, which makes these lipophilic compounds readily bioavailable to non-target species (Yebra *et al.*, 2004). Once these compounds are partitioned into cellular membranes, they disrupt essential metabolic and enzymatic functions, such as the energy-generation process through oxidative phosphorylation, leading to the death of the organism (Rittschof, 2001). At much lower concentrations, such as those present in marine systems far away from the TBT-source, these compounds also cause a series of sublethal effects the most famous of which is the endocrine disruption leading to sexual disorders such as imposex (the superimposition of a male characteristic in females; Rittschof, 2001; Omae, 2003; Yebra *et al.*, 2004). TBT-associated malformations have also been observed in many other species (i.e. abnormal shell growth in oysters) and the International Maritime Organization (IMO) also reports accumulation in mammals and debilitation of the immunological defences in fishes (Yebra *et al.*, 2004). The first bans against the use of TBT-based products commenced in France in 1982 and culminated in a proposed global ban through IMO (International Maritime Organisation) on the underwater use of organotin by 2008 (no TBT-bearing products could be applied after 2003; Omae, 2003; Yebra *et al.*, 2004). This proposal was finally

adopted on 5 October 2001, its entry into force being subject to ratification by at least 25 states representing 25% of the world's merchant shipping tonnage.

Even though such a ratification has not taken place up to date (only 10 countries representing 9.18% of the world tonnage have signed as at 31st January 2005 according to IMO), the use of TBT-SPC has been prohibited by regional and local legislations throughout the world, and such products have been effectively removed from the product assortment of the main marine paint companies (Yebra *et al.*, 2004). Ever since the first doubts about the harmful effects of TBT-compounds arose, paint companies commenced the development of alternative tin-free carrier systems, capable of dispensing Cu²⁺ and synthetic algaecides as a replacement of organotins (Yebra *et al.*, 2004). In this way, two main families of tin-free products reached the market (Yebra *et al.*, 2004):

- Those trying to imitate the polishing mechanisms of TBT-SPC through hydrolysable acrylate binders.
- Those trying to further improve rosin-based technologies in constant evolution since the early 20th century.

It was soon realised that developing a product with the same characteristics as TBT-based paints was no easy task, due to the dramatic influence of the pendant group in the performance of the acrylic-based paints (Vallée-Rehel *et al.*, 1998; Yebra *et al.*, 2004). As an example, after more than 10 years of tin-free research, copper-acrylate binders were still incapable of matching the long lasting performance of TBT-SPCs (Yebra *et al.*, 2004). In spite of the slow development process, very effective and long-lasting chemically-active AF coatings are currently dominating the AF paint market. Unfortunately, it has already been widely acknowledged that some of the tin-free biocide replacements do accumulate into the marine ecosystem (e.g. Irgarol 1051, diuron; Yebra *et al.*, 2004) so restrictive legislations are expected in the near future (Rittschof, 2001). Also copper, which is currently used in all the main AF technologies, could be soon subject to restrictions in their release rate into sea water (Rittschof, 2001) given the doubts about its environmental profile which are continuously being raised (e.g. Voulvoulis *et al.*, 1999; Katranitsas *et al.*, 2003).

In the light of this somewhat uncertain future for AF technologies based on metals and synthetic, environmentally-persistent, biocides, researchers have returned to the study of the biological basis of the fouling process in the search for environmentally-benign substitutes (Yebra *et al.*, 2004). The first and more evident idea is to look into AF compounds naturally present in the marine

ecosystem, and used by marine organisms to avoid being fouled themselves (Rittschof, 2001). The secondary metabolites under scrutiny include mainly terpenoids, steroids, fatty acids, aminoacids, heterocyclics (furans, lactones), acetogenins, alkaloids, and polyphenolics, some of them halogenated compounds with chemical structures that are unprecedented among terrestrial organisms (Rittschof, 2001; Yebra *et al.*, 2004). The enzymatic dissolution of the adhesives, the interference with the metabolism of the fouling organisms (e.g. nervous pathway interference), the inhibition of attachment, metamorphosis or growth, the promotion of negative chemotaxis, a repellent action, the alteration of the surface energy and, finally, the death of the organisms are some of the reported activity mechanisms associated with these compounds (Rittschof, 2001; Yebra *et al.*, 2004). As an example of the possibilities of these alternative active ingredients, the natural compound Bufalin has been found to be 6,000 times more effective than organotin in antissettlement activity (Rittschof, 2001). However, the chances of success of natural product-based AF coatings are limited due to (Rittschof, 2001; Yebra *et al.*, 2004):

- Difficulties in incorporating these biocides in active form into paint products (which may be solved by microencapsulation)
- Difficulties in releasing these compounds in a controlled manner
- Extremely long and costly biocide registration procedures
- Difficulties in large scale production of the compounds
- The presence of highly effective toxic coatings

Even though new natural AF compounds are still continuously isolated, the non-stick foul-release concepts is regarded by many as the most promising candidate to replace the current chemically-active AF coatings (Anderson *et al.*, 2003). The main reason for this is, probably, the fact that paint companies have managed to develop relatively successful foul-release coatings, so important marketing and research efforts are being focused on this AF technology. The non-stick, foul-release concept is based on low free surface energy coatings to which fouling species have difficulties in attaching. Furthermore, polydimethylsiloxane (PDMS) coatings, which are the most commonly used, also rely on the elastomeric properties of the backbone polymer and large coating thicknesses to release most of the fouling species that manage to settle onto the coating, at least at high sailing speeds (Anderson *et al.*, 2003; Yebra *et al.*, 2004). Nevertheless, it has been demonstrated that the free surface energy properties of these coatings are degraded over time by the conditioning film and the colonization of the surface by primary colonizers. In fact, slime fouling has been found to alter the initially smooth surface of the foul-release coatings

(Anderson *et al.*, 2003) eventually leading to larger drag resistances than chemically-active AF coatings (Holm *et al.*, 2004; Schultz, 2004). Additionally, the AF properties of pure PDMS are rather poor after relatively short immersion times, so foul-release coatings must incorporate leaching additives which can act as potent non-specific biocides (Rittschof, 2001), the environmental side-effects of which have not been fully assessed yet.

The following additional drawbacks are traditionally associated to foul-release coatings (Anderson *et al.*, 2003; Yebra *et al.*, 2004):

- Lack of adhesion to anti-corrosive primers
- Poor mechanical properties (prone to damage during service)
- Difficult application
- They must be cleaned frequently without damaging the coating
- High speeds are needed to release common fouling species
- High costs

In spite of these disadvantages, some of which appear to be already overcome (Anderson *et al.*, 2003), many successful case-stories of the use of foul-release coatings are available on fast-moving vessels and propellers (Anderson *et al.*, 2003). However, the existence of powerful broad-spectrum synthetic biocides with satisfactory degradation profiles in sea water (e.g. Sea-Nine® 211, Zn- and Cu- pyrithiones; Yebra *et al.*, 2004) means that chemically-active antifouling coatings will probably dominate the bulk market of AF paints for seagoing vessels for many years to come (Yebra *et al.*, 2004).

Finally, examples of other somewhat unsuccessful alternative AF ideas based on e.g. in-situ sea water electrolysis, piezoelectric effects, ultrasounds and magnetic fields are summarised in Callow (1990), Swain (1998), Bertram (2000) and Yebra *et al.*, (2004).

7.4 Characterization of Antifouling Paint

7.4.1 Paint Components

A paint is made up of several (typically 10-15) components. These can be divided into four main groups with different functionalities: binders, pigments, solvents, and additives. Not all paints have ingredients within every category.

Binder chemistry is varied and depends on the purpose the paint is going to serve. The binder is the single most important ingredient of a paint, which is the reason why many paints are named after their binder (e.g. epoxy or alkyd paint). Important functions of the binder are: film formation (i.e. holding the paint together) and adhesion to the substrate. In the case of antifouling paints, binders used are acrylics (with organometallic copolymers), natural rosin and rosin derivatives, and silicones (the latter being inorganic). Due to the fact that binders both come from natural sources (e.g. rosin) and organic synthesis (e.g. acrylics), the importance of problematic impurities vary. In the former case, a distribution of the rosin (various acids) is obtained and in the latter residual monomers can be a problem.

Pigments are most often used to provide a visual effect, mainly colour and opacity. Having achieved this, it is also important to ensure the pigment will remain essentially insoluble in the binder/solvent system in which it is used and will give the required physical properties, such as light fastness, weatherability, and resistance to chemicals (Lambourne and Strivens, 1999). The latter is particularly important for industrial paints (heavy-duty coatings such as an anticorrosive paint). Pigments can be either inorganic (e.g. TiO_2 , ZnO , and Fe_3O_4), or organic (e.g. Toluidine Red and Copper Phthalocyanine Blue). The inorganic ones are typically used for heavy duty coatings, where protection from the environment is more important than bright colours. Many inorganic pigments can be obtained from natural sources (e.g. ilmenite or titanium slag for TiO_2) including purification stages, but consistency is required and synthetic production is preferred where possible. Commercial organic pigments are all made synthetically (Lambourne and Strivens, 1999). Coating failures caused by the wrong choice of pigment are relatively rare (Weldon, 2002). Impurities (often salts) in the pigments can, however, be a source of failure (e.g. blistering caused by the establishment of an osmotic cell in humid or wet environments).

The pigment phase holds potential for manipulation of the paint properties. For example, in antifouling paints, seawater-soluble pigments play an active role in the paint behaviour (see e.g. Kiil *et al.*, 2002 and later sections on mechanisms). Extenders (fillers) are coarse particles (e.g. natural limestone or clay). They are cheap and added for economic reasons, but also provide strength and resistance to the paint.

Solvents are added to a paint to enable the, to control the flow of wet paint on the substrate, and to obtain an even and smooth film on the substrate in a suitable time upon evaporation. These properties are rarely met by one solvent alone and typically mixtures of solvents are used. Except for water, all solvents

used in organic coatings are organic compounds of low molecular weight. Xylene is a typical example.

Additives are present in a paint in small amounts (typically less than 5 wt %), but can have a marked effect on the paint properties. They include antifoam, antisetling, and antiskinning agents, can-corrosion inhibitors, driers, dispersion aids, and many more. Details of these can be found in many books (e.g. Lambourne and Strivens, 1999).

7.4.2 *Product Design Criteria of an Antifouling Paint*

Before a specific paint is formulated it is important to define the characteristics of the paint. What type of paint is it? Where will it be used? On which substrates will the paint be applied? Should it be applied by air spray or brush? What type of environment will the paint be exposed to (e.g. rain, sea water, sunlight)? Are there any requirements to drying or hardness of the paint? Any legislation which will have to be taken into account? Legislation can be on amounts or release rates of specific ingredients in the paint (e.g. active ingredients in antifouling paints, see later sections). It can also be on the Volatile Organic Compounds (VOC) which is related to the solvent emissions from the paint. What are the maximum acceptable costs of the raw materials used?

The answer to all these questions defines the design criteria for the specific product. In the end, the final formulation will be a compromise between the criteria mentioned above. When the design criteria have been settled, the actual formulation can commence. Not surprisingly, industrial paints or coatings need to be more versatile than household paints. Their prime purpose is to provide protection from the environment. In the case of a chemically active antifouling paint this means, overall, that it must:

- Resist biofouling for 3-5 years (i.e. leach biocides at a relatively stable and very slow rate)
- Show appropriate sprayability and drying under different weather situations
- Show good adhesion properties to the underlying paint layer or substrate
- Be flexible enough to avoid cracks
- Resist impact from fenders and high pressure from keel blocks
- Provide an as-smooth-as-possible hull surface so as to save fuel

The design criteria are met by a correct paint formulation. This is discussed in a later section.

7.4.3 Full Paint System on a Ship

Painting a vessel's underwater hull serves two main purposes:

- protection of the construction steel
- prevention of undue hull roughness

As discussed in the section on consequences of biofouling, an increased hull roughness will inevitably lead to increased resistance to movements of the vessel, causing lower service speed or increased fuel consumption. The hull roughness increase is mainly due to the settlement of marine organisms or due to mechanical damages, corrosion etc. When preventing corrosion of ship hulls, the principle of creating a physical barrier that keeps out ions and retards the penetration of water and oxygen is employed. This anticorrosive barrier coat or primer is the first coat to be applied on the steel substrate. In the case of new buildings a shop primer may, however, partly precede such a coat. A shop primer is a thin anti corrosive coat (20 – 30 μm) which provides a temporary protection to the steel plates during ship building. In the final hull surface, a barrier effect is obtained by applying thick coatings of paints with very low water permeability. These paints are nowadays usually based on epoxy binders and they are typically applied in 2 or even 3 turns to obtain a final thickness of 250-500 μm . By adding flake formed pigments e.g. leafing aluminium or micaceous iron oxide, a barrier effect can be achieved at a lower film thickness. However, if an anticorrosive coating is damaged, the areas of damage lie open for corrosion, which can proceed both down into the steel and outwards under the intact coating (under rusting). Thus, where there is a risk of mechanical damage, additional protection, in the form of cathodic protection (e.g. zinc anodes or impressed current) is often provided.

Normally an antifouling paint does not adhere well enough directly on to the epoxy primer. Therefore a so called tie coat is usually applied before the antifouling coating system. The tie coat is typically based on a technology with properties which are compatible with both the chemically-curing epoxy primer and the physically-drying antifouling paint. Finally the antifouling paint is applied. The specific type of antifouling paint is determined from the expected trading pattern of the vessel. Low speed and low activity requires a faster polishing paint type to provide the correct amount of leached biocide and high

speed and high activity on the other hand requires a low polishing type, see Figure 5. The temperature and fouling intensity also have to be taken into consideration before the antifouling paint is specified. Depending on the type and trading pattern the total thickness of the AF system typically is in the range from 200 to 400 μm and typically applied in 2 to 3 turns.

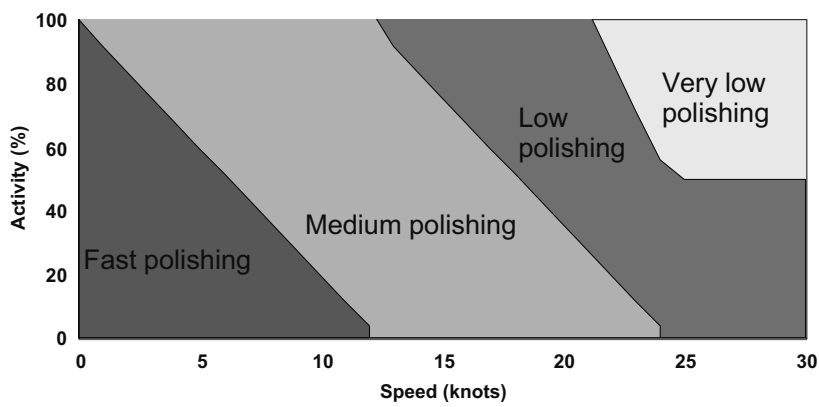


Figure 5: AF paint specification as a function of trading speed and activity. The activity accounts for the amount of time in which the vessel is not idle.

The total paint system of a typical underwater ship hull is shown in Figure 6.

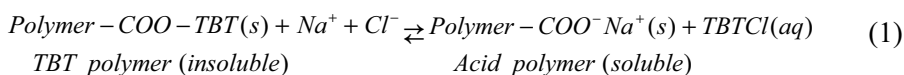


Figure 6: A sketch showing the different layers in a paint system used on the underwater hull of a ship. Usually the whole system is composed of 5-6 layers.

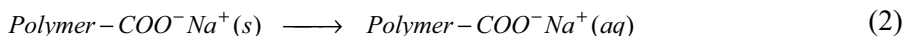
7.4.4 Working Mechanisms of Antifouling Paints

To explain the working mechanisms of an antifouling paint we will here use the well-known tributyltin (TBT)-based paint. The reason for this is that this paint type has been thoroughly characterised over the years (Kiil *et al.*, 2001, 2002a,b,c, 2003). Other modern antifouling paints appear to have similar working mechanisms (Yebra *et al.*, 2004).

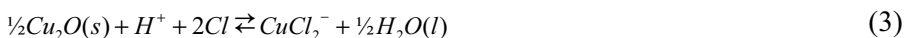
The copolymer used in the binder phase of TBT-based antifouling paints, which can undergo hydrolysis in seawater, is that of tributyltin methacrylate (TBTM) and methyl methacrylate (MMA). Typically, another copolymer is present in smaller amounts. This compound is known as a retardant and can be butyl methacrylate/methyl methacrylate (BMA/MMA). This component is not reacting with ions present in the seawater and is present to reduce the solubility of the hydrolysed TBT-polymer and to give strength to the polymer matrix, thereby reducing the polishing rate of the paint system. The two copolymers are completely miscible and form a one-phase binder system. The self-polishing mechanism of the polymer begins with the following reversible reaction in seawater (Kiil *et al.*, 2001)



After some time, the partially-reacted outer layer of the polymer film, now containing hydrophilic free carboxylate groups, has little strength and is easily eroded by moving seawater (self-polishing effect), exposing a fresh layer of organotin acrylate polymer



The hydrolysis and erosion mechanism is continually repeated until no polymer is left. Seawater-soluble pigment particles, such as Cu_2O and ZnO , dissolve near the surface of the paint film. As an example, the reactions of Cu_2O to form CuCl_2^- and CuCl_3^{2-} are provided:



The overall mechanism of a TBT-based antifouling paint exposed to seawater is shown schematically in Figure 7. For simplicity, no inert pigments (such as TiO_2) are shown in the figure.

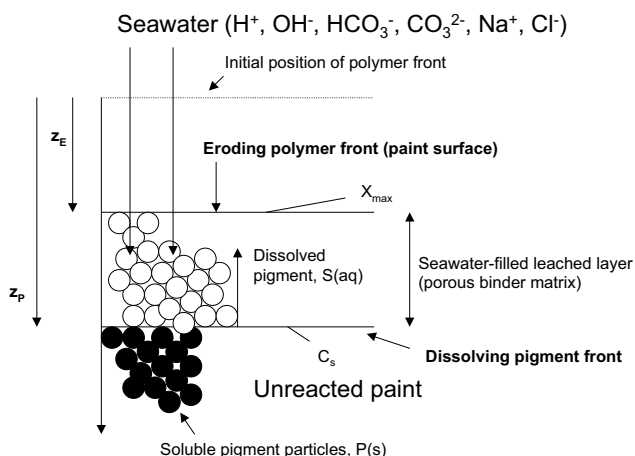


Figure 7: Schematic illustration of a self-polishing antifouling paint with soluble Cu_2O particles exposed to seawater (no insoluble pigments present for simplicity). Notice the pigment-leached layer and the two moving fronts (eroding polymer front, z_E , and dissolving pigment front, z_P). After Kiil *et al.* (2002c).

Moving seawater slowly erodes the copolymer through hydrolysis, thereby releasing the TBT-groups as TBTCl . At the surface of the paint, the TBT-binder reaches a certain conversion termed X_{max} at which conversion the polymer erodes. Seawater diffuses into the porous polymer matrix, ahead of the eroding polymer front, and dissolves the pigment particles, at the dissolving pigment front, resulting in the formation of a leached (i.e. Cu_2O and perhaps ZnO depleted) layer. The dissolved copper forms a complex with Cl^- (CuCl_2^- or CuCl_3^{2-}) diffuses out through the seawater-filled leached layer and across the external solid-liquid boundary layer into the bulk seawater. Consequently, two moving fronts, the dissolving pigment front and the eroding polymer front, develop. After some time, due to the strong coupling of the rate of movements of the two fronts (Kiil *et al.*, 2002b), the thickness of the leached layer becomes constant (stable).

Summarising, the paint-seawater mechanism includes the following rate-influencing steps: hydrolysis and erosion of the active TBT-polymer binder, effective diffusion in the leached layer of dissolved pigment species and TBTCl ,

and external mass transport of relevant components. All the rate-processes are coupled.

7.4.5 Formulation and Paint Production

The basic constituents in a self-polishing antifouling paint are 1) the binder system, 2) the biocides and pigments and 3) the solvents.

7.4.5.1 Binder System

The binder provides the film forming properties and cohesive strength in the paint and, at the same time, it offers the built-in self-polishing action in sea water.

7.4.5.2 Biocides

The amount of biocides needed in an antifouling paint will be determined by actual tests performed in real life. A rule of thumb says that the minimum level of protection with copper is a leaching rate of $10 \mu\text{g}/(\text{cm}^2 \cdot \text{day})$ (WHOI, 1952). The amount of cuprous oxide can be up to 40 wt % of an antifouling paint and it is normally assisted by booster biocides (5 to 10 wt %) to provide full protection against both animals and algae. The amount of biocides will be based on practical performance and, at the same time, be restricted to given legislation.

7.4.5.3 Solvents

The amount and types of solvent will depend on the requirements to VOC and the type of polymer (binder) to be dissolved in the paint. Another important parameter is the sprayability of the paint which also depends on the type and amount of solvents.

In principle the three main constituents mentioned above form an antifouling paint product. However, a number of other paint properties have to be fulfilled as well.

7.4.5.4 Pigment volume concentration (PVC)

First of all the PVC is very important. PVC is defined as the volume of pigments divided by the volume of pigment plus dry binder (i.e. no solvents included). CPVC is the abbreviation for critical pigment volume concentration. CPVC is the pigment concentration where the pigments are packed as close as possible and the binder is exactly the amount required to fill the space between the pigments. When formulating paint, the PVC should normally be lower than the CPVC. If not, the cohesive strength of the dry film is very low giving the risk of mechanical failures.

7.4.5.5 Wetting agents

The most critical unit operation in paint production is the grinding and dispersion of pigments. Pigments tend to collect in agglomerates and in the dispersion process the agglomerates are exposed to high shear forces in a dissolver or pearl mill. The dispersion process can be assisted by wetting agents which are added to ensure a proper wetting of the pigments before the grinding process.

7.4.5.6 Thixotropic agents

Thixotropic agents are added to give the paint the correct rheologic properties such as viscosity and sag resistance (sagging is defined as the downward movement of a paint film on a vertical surface during curing, resulting in an uneven coating having a thick lower edge) and to prevent settling of the pigments during storage. The viscosity is measured by several different methods: e.g. Stormer viscosity or flow cup. These methods are either based on measuring the viscous forces acting on a rotating cylinder in the liquid or by the time for a liquid to leave a cup through an orifice respectively. Measured by a Stormer viscometer, antifouling paints will typically have a viscosity between 65-95 KU (i.e. 4-14 poise; KU means Krebs Units, which is an arbitrary viscosity unit for a Stormer viscosity instrument). The minimum sag resistance value (the unit is microns) of an antifouling paint should be around 500 microns for commercial vessels and about 300 microns for yachts (based on wet film thickness).

It is not possible to give an exact procedure of how to formulate paint. As mentioned above, it will be a compromise between the mentioned criteria and

the final formulation will normally be the result of a number of iterative suggestions. Figure 8 shows a sketch of a possible course.

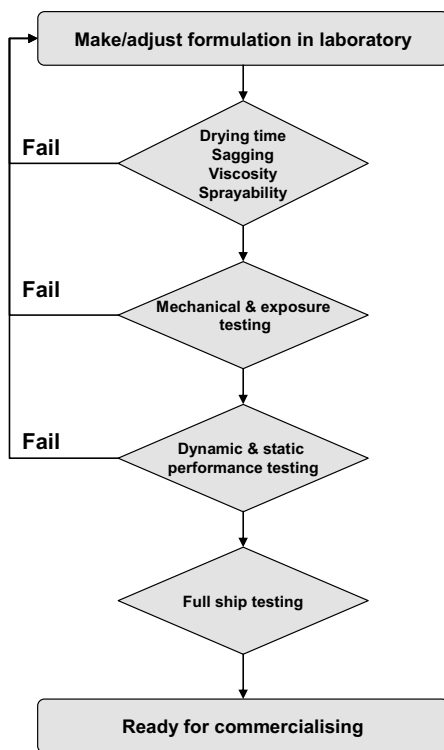


Figure 8: A possible course in the development of an antifouling paint.

7.4.5.7 Paint production

The most critical unit operation in paint production is the grinding and dispersion of pigments. In factory production, paints will usually be produced in hi-speed dispersers and pearl mills to create the high shear forces needed to disperse the agglomerated pigments. The high speed disperser is used for mixing the ingredients and can also to some extent grind the pigments. Pearl mills are used for grinding the pigments into smaller particle sizes.

In the laboratory, the production of paint is normally done either by high speed dissolvers in combination with glass beads or by using a so called "Red Devil" where all the ingredients are placed in a closed container together with glass

beads and then shaken. The fineness of grinding is controlled during the grinding process.

During the production of paint, it is important to keep control of the temperature. Due to the high shear forces a substantial amount of heat is produced especially in the pearl mill. Some ingredients in the paint are sensitive to heat, e.g. solvents which will have the risk to flash off. Therefore additional cooling is normally needed in this operation. Figure 9 shows a flow diagram of paint production in a factory.

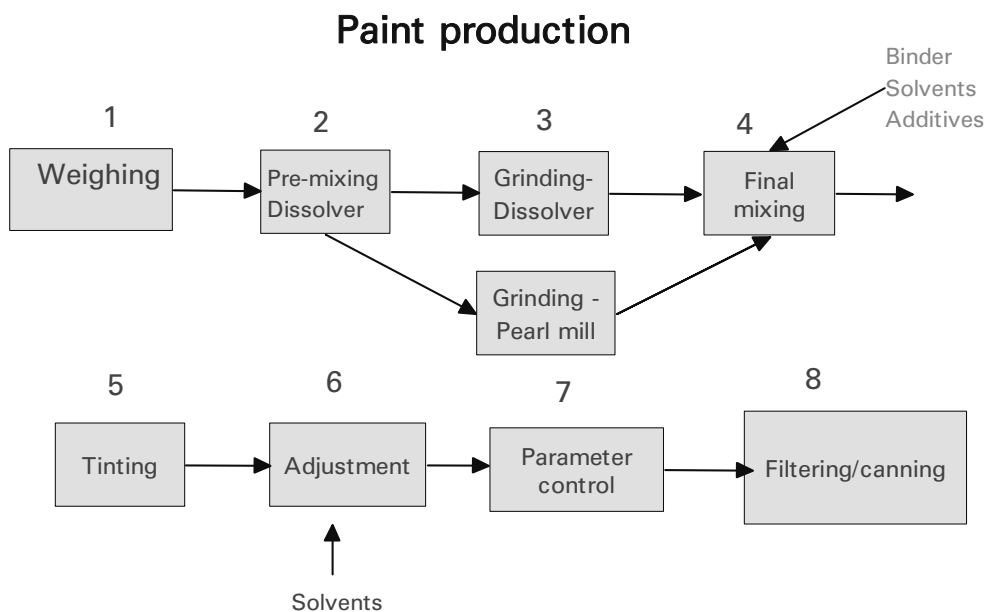


Figure 9: Typical flow diagram describing full scale paint production.

In Fig. 9, Step 1 is to collect and weigh all the needed raw materials. In step 2, the pigments and part of the binder are pre-mixed together with wetting agents to create a grinding base. In step 3, the pigments are grinded (dispersed) by the dissolver and, if needed, also by the pearl mill. In step 4, the rest of the binder, solvents and additives are added and it is followed by tinting (if special shade is needed), viscosity adjustments, quality control and canning.

7.4.6 *Painting Ship Hulls*

Ships belong to the largest moving structures ever made. For example Very Large Crude Carriers (VLCC) can be up to 500 m long and 60 m wide which means that the exposed area of the outer hull in some cases will exceed 50.000 m² and the exposed area in e.g. the ballast tanks will be even larger - up to 230.000 m². This implies the need for an enormous amount of paint. The vessel should be designed so that it is solid and robust and in a way so it can be maintained properly.

The first steps in the construction of new vessels are welding together plates and profiles into block sections. The blocks are then either coated with the full paint system with only a temporary anticorrosive system and then transported to the slipway or the building dock where they are erected and assembled, see Figure 10. In the former case (where the blocks are full painted in the paint shop) the edges between the blocks to be welded together have to be free from paint for about a few centimetres. After welding the affected zones are then coated with the full coating system. In the latter case (where the blocks only are given a temporary anti-corrosive protection system in the paint shop) the blocks are welded together and the whole vessel is then coated with the full system.



Figure 10: The block sections are assembled in the building dock. The sections have been given a full paint system before assembling. Note the paint free zone where the sections are welded together.

The protection time of a self-polishing antifouling system is typically up to 5 years. At the end of the service period, a ship has to go into dry dock for maintenance, renewal of the antifouling system and touch up or even renewal of the anticorrosive system. Typically maintenance of the outer hull involves removal of fouling, leached antifouling paint, defective paint layers, rust, salt, slime and oil, and restoring of the paint system on the defective areas. Barnacles (hard shell fouling) are normally removed by scraping and then the underwater hull is cleaned by means of high-pressure fresh water washing. This treatment will remove slime, algae, flaking and poorly adhering paint and, to a minor extent, loose rust. If necessary, the hull can be cleaned using a suitable detergent (e.g. in case of oil contamination). As soon as the hull is dry, it is inspected for any adhering rust flakes, blisters, paint cracks and other damages which should be rectified. The choice of cleaning method depends on the type and extent of damage. Abrasive blasting or power tool cleaning are typically chosen. After cleaning, the treated areas are touched up with anticorrosive paint and, as soon as possible, the chosen antifouling system is applied. As mentioned earlier a tie coat between the anticorrosive and the first antifouling coating is normally applied. More details on marine painting can be found in e.g. Berendsen (1989).

7.5 Paint Testing

The painting of structural steel and ships exposed to the marine environment offers some of the heaviest challenges with respect to protection against corrosion and, in case of immersed systems, against marine fouling. Durability, or the ability to remain unaffected, is the keyword covering the paint systems used in this harsh environment. Salt-water exposure, partial immersion, drying out periods and changing temperatures are some conditions which pose stress on a protective paint system having an enormous effect on the durability of the paint. Therefore, when developing and monitoring the performance of paints, test methods which simulate the actual usage are always adopted. In the paint industry, test method specifications have been drawn up by a number of national and international organisations such as the International Standards Organisation (ISO) and the American Society for Testing Materials (ASTM). In the following, some of the test methods of special interest for antifouling systems are described. The test methods all include full painting system on steel substrate, say anticorrosive paint, tie coat and antifouling top coat (except for the testing performed on laboratory rotors, described in subsequent sections where a polymer substrate is used).

Antifouling performance testing is a very important and specific method for these types of paints. For several years, Hempel A/S has conducted both static and dynamic tests in the evaluation and optimisation of biocide-based AF paints and fouling-release paint products.

7.5.1 Mechanical Testing

In this section, methods involving impact, indentation, bending and adhesion will be described. Several of the standard methods include damage of the steel substrate as well as the paint, and ideally a coating system should be able to absorb this deformation without failures such as peeling and cracking. However, in real life, compromise between hardness and flexibility is always necessary to meet the adequate properties. The tests are either applied to freshly applied paint systems or to systems aged in exposure equipment which simulate accelerated weather situation (elevated temperature, alternating dry and wet conditions).

7.5.1.1 Adhesion test

Adhesion test is used to evaluate the adhesion of a paint system to the substrate and between coats (layers). The test can be performed by one or a combination of three methods:

X-cut: According to ASTM D 3359, method A, an X is cut into the film to the substrate, pressure tape (TESAPACK 4287) is applied over the X and then removed, and adhesion is evaluated by comparison with descriptions and pictures. The method is used to establish whether the adhesion failure of the coating to the substrate may occur between the coats (adhesive break) or in the coating (cohesive break).

Cross-cut (#-cut): According to ASTM D 3359, method B (ISO 2409), a lattice with 6 cuts in each direction is made in the film to the substrate. Then, pressure tape (TESAPACK 4287) is applied over the lattice and then removed, and adhesion is evaluated by comparison with descriptions and pictures. The method is used to establish whether the adhesion of the coating to the substrate may occur between the coats (adhesive break) or in the coating (cohesive break).

The spacing of cuts depends on the thickness of the coating and of the type of substrate.

2 mm spacing: Not suitable for dry films thicker than 125 microns.

3 mm spacing: Not suitable for dry films thicker than 250 microns.

Knife test (KNF): The test is done by making two intersecting scratches through the paint film to the substrate with a sharp steel knife. Adhesive or cohesive failures are evaluated by peeling the coating from the intersection point and outwards. Common for the three adhesion evaluation methods are that the test is performed on immersed and non- immersed panel-half (referred to as respectively "wet" and "dry" adhesion). The type of rupture is reported, and the severity is judged on a scale from 5 (perfect) to 0 (poor).

Pull-off Test: Pull-off test according to ISO 4624 (ASTM D 4541), with P.A.T hydraulic adhesion tester. The standard conditions are 1.58 cm² dolls and Standard Araldit glue, cured for 24 hours. This test covers the determination of the pull-off strength of a coating or coating system, by determining the greatest perpendicular force (in tension) that a surface area can bear, before a plug of material is detached. Failure will occur along the weakest plane within the system comprised of the test fixture, adhesive coating system and substrate. After the proper curing time of the glue, the paint film is cut free around the dolls down to the substrate and the dolls are pulled off. The pull-off value (tensile strength) is noted, and converted in relation to the area of the doll in MPa. The type of rupture is also noted (cohesive/adhesive).

7.5.1.2 Impact

Impact (effect of rapid deformation), according to ISO 6272-1, Falling-weight test, large-area indenter using an Erichsen Impact Tester. This test method covers a procedure for rapidly deforming by impact a coating film and its substrate and for evaluating the effect of such deformation. The test is performed on 1.5 mm panels. After the coatings have been cured, a falling-weight of 1 kg, with an indenter-head of 20 mm Ø, is dropped from a distance, in meters, onto the test panel. The panel is supported by a steel fixture, with a hole of 27 mm Ø, centred under the indenter. When the indenter strikes the panel, it deforms the coating and the substrate. By gradually increasing the distance the weight drops, the point at which failure usually occurs can be determined. The impact value is reported as the highest impact, reproduced 5 times, which results in no visible cracks and no adhesion failure in the paint

film. The impact value is stated as $\text{kg}\cdot\text{m}$. A possible rupture is evaluated as cohesive or adhesive.

7.5.1.3 Mandrel bending test

Mandrel bend test according to ISO 1519-1973 (ASTM D 522-88 method B). The test method covers the procedure for assessing the resistance of a coating of paint, varnish or related product to cracking and/or detachment from a metal substrate (with a thickness of 250 microns) when subjected to bending round a cylindrical mandrel under standard condition. When the panel has been coated, cured for 4 weeks and cut to size, the test panel is placed over a mandrel with the uncoated side in contact and with at least 50 mm overhang on either side. Using a steady pressure of the fingers, bend the panel approximately 180° around the mandrel. Remove and examine the panel immediately for cracking visible to the unaided eye. If cracking has not occurred, repeat the procedure using a smaller diameter on untested panels of a specimen until failure occurs or until the smallest diameter mandrel has been used.

7.5.1.4 MAN-H - Hydraulic mandrel bending test

This mandrel bend test is a slight modification of ISO 1519-1973 (ASTM D 522-88 method B), allowing the paint systems to be applied on thicker steel panels which can be prepared in accordance to the product data sheet. The test method covers the procedure for assessing the resistance of a coating of paint, varnish or related product to cracking and/or detachment from a metal substrate when subjected to bending round a cylindrical mandrel under standard condition. When the panel has been coated and cured for 4 weeks, the test panel is placed over a mandrel with the uncoated side in contact and with at least 50 mm overhang on either side. Using a hydraulic pressure with constant velocity, bend the panel around the mandrel. Remove and examine the panel immediately for cracking. If cracking has not occurred, repeat the procedure using a smaller diameter on untested panels of a specimen until failure occurs or until the smallest diameter mandrel has been used. Record the diameter of the smallest mandrel at which the coating does not crack.

7.5.1.5 Wooden block settings

When ships are in dry dock, they are supported by wooden blocks. When antifouling is applied, these wooden blocks are sometimes moved in order to apply antifouling to the areas where the wooden blocks were. The blocks are

moved to areas with freshly painted antifouling. The pressure underneath the wooden blocks is around 70 kg/cm², which means that if the paint is not dry enough, the paint will ooze out from underneath the wooden blocks. This test determines how quickly the blocks can be moved without oozing. The paint system to be tested is affected by specified pressure in 3 minutes. If pressure is not specified, the test pressure is 70 kg/cm² (a 3 cm² wooden block is used). The test is repeated 24 hrs, 48 hrs, 72 hrs, etc. after application of the last coat until an acceptable level of deformation is obtained.

7.5.2 *Accelerated Exposure Testing*

This section describes some of the most common exposure tests or ageing procedures applied to antifouling systems. The ageing processes are normally succeeded by adhesion or pull off tests described in section 5.1.

7.5.2.1 *Blister box test*

Blister Box Test, according to ASTM D 4585 (ISO 6270). This test evaluates the water resistance of a coat by condensation of water vapour. The panel surface with the coating system is exposed to 40°C, saturated water vapour, at an angle of 15° to the horizontal. The reverse side of the panel is exposed to room temperature. At each inspection blisters and rust are evaluated according to ASTM D 714 (ISO 4628-2) and ASTM D 610 (ISO 4628-3) respectively. Cracking is evaluated according to ISO 4628-4. When the test is stopped, adhesion is evaluated according to ASTM D 3359, tape test (ISO 2409) or ASTM D 4541 (ISO 4624), pull-off test.

7.5.2.2 *Cyclic blister box test*

According to ASTM D 4585. This test evaluates the water resistance of a coat by condensation of water vapour. The panel surface with the coating system is exposed to saturated water vapour, at an angle of 60° to the horizontal. The reverse side of the panel is exposed to room temperature. The apparatus can be set to continuous condensation or run in a cyclic-condition, changing between condensation and drying. The evaluation is the same as with standard Blister Box Test.

7.5.2.3 Immersion

Immersion according to Hempel Method. Half the panel immersed in fresh water and half the panel exposed to vapour. Possible weak adhesion is hereby provoked. The panels are applied, cured for 7 days and immersed in potable water for 2 weeks. After exposure the panels are immediately examined for blistering and adhesion (Knife test, X-cut, #-cut).

7.5.3 Dynamic Testing using Rotary Set-up

The dynamic testing is performed on rotary set-ups either located in the laboratory or at sea sites. Typically, the laboratory set-ups have been used to investigate the polishing and the leaching behaviour of antifouling paints and the information has been used either for screening purposes or for support for mathematical modelling of paint behaviour (Kiil *et al.*, 2001).

Figure 11 shows a rotor (Hempel A/S) located in the Mediterranean Sea close to Barcelona (Catalunya, Spain). The paints to be investigated are placed on the drum (about 1 m in diameter) which is then immersed into the water and rotated. The rotational speed is adjusted to the desired value, typically between 15 to 20 knots. The panels are evaluated after given periods: the type and extend of fouling, cracking and peeling is determined and the remaining paint layer thickness is measured. The paint layer thickness is used to calculate the rate of polishing (dissolution of paint). The duration of the full testing is normally 2 years. In the Mediterranean Sea the blooming season of algae is in the spring. This period is very important in relation to antifouling performance evaluation.

Figure 12 shows a laboratory rotor (Hempel A/S) located in Copenhagen (Denmark). Immersed surfaces are tested on the rotary rig which consists of two concentric cylinders with the innermost in rotation. The cylinder pair is immersed into a tank containing about 400 liters of artificial sea water where the temperature is controlled using a heat exchanger. In this type of configuration the intention is to create a close approximation to Couette flow (flow between two parallel walls, where one wall moves at a constant velocity). For both laminar and turbulent Couette flow, the shear stress will be constant across the channel width provided that the spacing between the cylinders is sufficiently small. The samples to be tested are applied on the surface of the inner cylinder (diameter and height of 0.3 m and 0.17 m, respectively) and then immersed into the centre of the static cylinder (diameter and height of 0.38 m and 0.17 m, respectively). The rotational speed is adjustable to almost any

relevant speed (speeds around 20 knots are typically employed). The sea water is artificially composed with sodium, chloride, sulphate and magnesium being the main constituents. The advantage of laboratory testing compared to sea rotor testing is the ability of keeping the operational parameters, such as the temperature, salinity and pH well defined. Therefore, the laboratory rotors are normally used for precise and fast evaluation of the leaching and polishing behaviour established by microscopical examination of the paints (see later section).



Figure 11: A Hempel A/S sea rotor in Barcelona. The researcher is measuring the film thickness of an antifouling paint system.



Figure 12: A laboratory rotor used for precise and fast polishing and leaching evaluation.

7.5.4 Drag Resistance

Laboratory rotors have been used to evaluate the drag resistance of immersed surfaces as well. The rotational frequency of the innermost cylinder is adjusted to the relevant speed (monitored by a tachometer) and after about 30 minutes of flow stabilisation a 50 Nm strain gauge transducer picks up the torque, M_t . All measurements are based on the average of three replicate tests. A sketch of the set-up is shown in Figure 13; details on the set-up and calculations are described in Weinell *et al.* (2003).

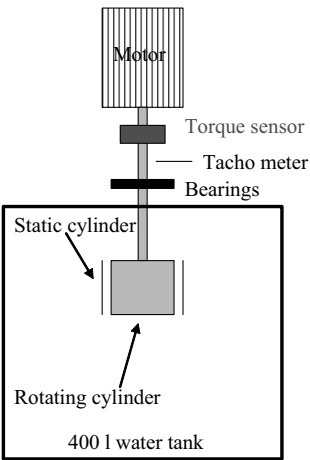


Figure 13: The set-up for evaluation of drag resistance of immersed surfaces.

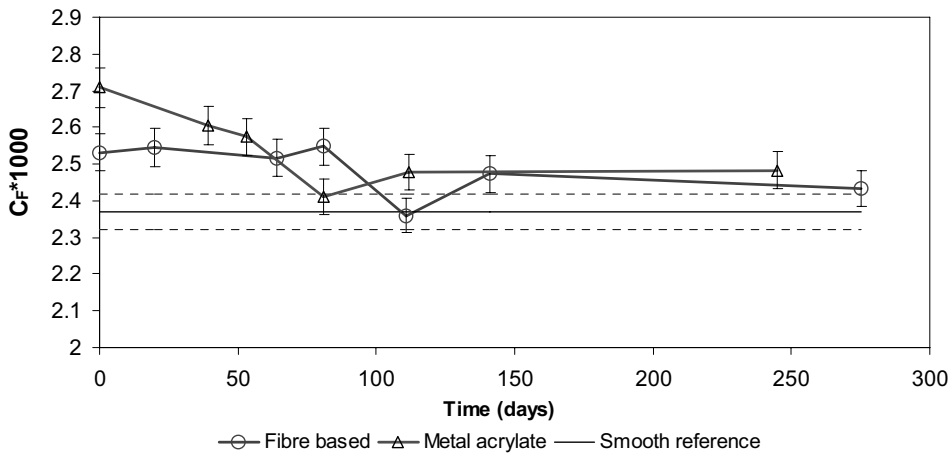


Figure 14: The friction coefficient at 35 knots of two different antifouling technologies and a hydrodynamic smooth reference plotted vs the ageing time. Modified from Weinell et al. (2003).

Figure 14 shows an example from the laboratory studies where two different antifouling technologies are compared to each other. Samples of a fibre based zinc resinate technology and a metal-acrylate antifouling technology were aged in a rotary set-up (30 °C, 30 knots). The friction coefficients have been measured at 35 knots as a function of ageing (up to approx. 275 days). The friction coefficient becomes smaller and closer to a hydrodynamic smooth reference. After a couple of months, there is no significant difference between

the friction coefficient of the fibre based technology and the smooth hydrodynamic surface confirming that the paints are self-smoothening.

7.5.5 *Static Performance Testing*

The behaviour of antifouling products is tested under static condition (in the sea) as well as under dynamic conditions. Hempel A/S has chosen two different locations for that purpose: in the Mediterranean Sea (sub tropical environment) and in the waters around Singapore (tropical). It appears that the fouling intensity of especially algae is very high in the Mediterranean Sea, whereas the animal fouling is very aggressive in Singapore. This gives a unique opportunity to test the antifouling performance under different stress conditions. Combining the experience from both the dynamic and the static testing gives the opportunity to predict the behaviour of the paint on a vessel which experiences both static and dynamic conditions. Figure 15 shows a rack from static immersion in the Mediterranean Sea.



Figure 15: Rack from static immersion in the Mediterranean Sea.

7.5.6 Full Ship Testing

The final performance testing consists of test patches or full ship application. The specific paint is applied in a ship yard (see chapter 4) and in case of test patch the area is typically 100 m². Inert spots are also applied for the later MEP evaluation. A diver is sent to the specific vessel carrying the test patch and he is making a performance report with information on fouling intensity (on both the antifouling paint surface and on the unprotected inert spots), detachments, blistering, cracking, other damages etc. Samples are then taken and analysed back in the laboratory (see section 7.5.8). Figure 16 shows a picture of a vessel being applied with a test patch.



Figure 16: A vessel being applied with an antifouling test patch.

7.5.7 Biocide Release Measurements

Biocide release rate methods were first developed for TBT-containing compounds in an effort to establish limits on their release from AF into marine bodies (Haslbeck and Holm, 2005). The core idea of this kind of methods is to develop standardised procedures which can tell, after as short an experimental time as possible, whether an AF coating will be leaching environmentally acceptable amounts of biocide into sea water. Two such methods are available to measure the release rate of copper, namely the ASTM D6442 and ISO 15181-

1&2 (Arias, 1999; Haslbeck and Holm, 2005). Both methods are based on a painted polycarbonate rotating cylinder immersed into a holding tank in which artificial sea water of known composition is kept at relatively constant conditions (see Table 1). At specific time intervals, the cylinder is immersed into a 1.5 litre tank where they are rotated for typically 1 hour, after which the total copper released is determined. In this way, copper release rate vs. time curves are obtained. Typically, the average release rate value between day 21 and 42/45 and the accumulated release rate during the first 14 days of exposure are used to compare the different paint systems.



Figure 17: Preparation steps for the coated polycarbonate cylinders (top): (1) blank; (2) tape applied; (3) painted by airless spray; (4) tape removed. Rotating equipment (bottom)

When round robin tests were performed to test the reproducibility of these standard procedures, large coefficients of variation between laboratories were obtained for tin-free paints (78-80% and 24-32% for the ISO and ASTM methods respectively; Haslbeck and Holm, 2005). These discrepancies have multiple sources such as the analytical method (Haslbeck and Holm (2005) report 4-54% deviations when different laboratories measuring samples of known concentration), the sea water conditions both in the holding tank and the measuring tank (Haslbeck and Holm, 2005), the sample preparation for analysis

(Haslbeck and Holm, 2005), and the potential deposition of inorganic copper salts (Arias, 1999). Standardised methods have also been demonstrated to overpredict in situ release scenarios (Valkirs *et al.*, 2003). Quoting Haslbeck and Holm: with the current methods "it will be difficult to interpret and predict release rate results and to estimate how reformulation of coatings or limits placed on release rates would impact the environment". Thus, it seems that further work is needed in order to optimise these methods.

Table 1: Comparison between the new, unified ASTM and ISO standard test methods for copper release rates of AF coating systems in sea water (to be implemented during 2005; Arias, personal communication). The description of the original procedures (ASTM D6442-99 and ISO/DIS 15181-1,2) can be found in Arias (1999) and Haslbeck and Holm (2005).

	ASTM D 6442-99	ISO/DIS 15181-1,2
Panel type (no. replicates)	Polycarbonate (3 replicates)	Polycarbonate (2 replicates)
Painted area	200 cm ²	200 cm ²
Reference cylinders	1 uncoated	1 uncoated + 1 reference paint
Drying conditions	7 days at 23-27 °C	at least 7 days (ISO 3270)
Paint film thickness	min 100 µm thickness; min 50 µm after test	min 100 µm thickness; min 50 µm after test
Application method	Sponge or spray (unless manufacturer only specifies spray)	After manufacturer's instructions
Release rate measuring container		
<i>material</i>	polycarbonate container	polycarbonate container
<i>dimensions</i>	(Diameter: 13.5, Height: 19 cm)	(Diameter: 12-15, Height: 17-21 cm)
<i>sea water volume used</i>	3 baffles (Diameter: 6mm)	3 circular rods (Diameter: 4-8mm)
<i>sea water characteristics</i>	1.5 litres	1.5 litres
<i>temperature</i>	synthetic sea water (ASTM D 1141)	synthetic sea water ISO 15181-1. Only 7 salts
<i>pH</i>	25 °C ± 1	23 °C ± 1
<i>salinity</i>	7.9-8.1	7.9-8.1
<i>time rotating</i>	33-34 ppt	32-34 ppt
<i>cylinder rotating device</i>	1 hour. Shorten if Cu exceeds 200 ppb. Revert to 1 hour as soon as possible thereafter	1 hour. Shorten if Cu exceeds 100-200 ppb
<i>test frequency after (days)</i>	60 rpm ± 5 (0.4 knots; diameter 65 mm)	0.2 m/s rpm ± 0.2 (0.4 knots)
<i>cylinder diameter</i>	1,3,7,10,14,21,24,28,31,35,38,42,45	1,3,7,10,14,21,28,35,42
	65 mm	65mm ± 5
Holding tank		
<i>sea water characteristics</i>	synthetic sea water (ASTM D 1141)	synthetic sea water ISO 15181-1
<i>temperature</i>	25 °C ± 1	22-24 °C
<i>pH</i>	7.9-8.1 (adjust 0.1N HCl or 0.1N NaOH)	7.9-8.1 (adjust 0.1N HCl or 0.1N NaHCO ₃)
<i>salinity</i>	33-34 ppt	32-34 ppt
<i>Maximum level of biocide</i>	carbon filters: 2-8 turns over 1 h	carbon filters+ chelating ion exchange resin: 6-8 turns over 1 h
<i>initial water biocide content</i>	100 ppb Cu	100 ppb Cu
<i>temperature and pH monitoring</i>	No limit; correct for any copper found.	10 ppb
<i>salinity monitoring</i>	every 1-2 days	Daily
	weekly	every 1-2 days
Leaching rate measurements	Any method with a detection limit ≤ 6 ppb	Any method with a detection limit ≤ 10 ppb

7.5.8 Optical & Scanning Electron Microscopical Examination of Paint

7.5.8.1 Microscopical examination of paint (MEP)

During paint testing, one of the most important parameters to monitor is the rate at which the paint surface polishes. Too low a polishing rate usually results in thick leached layers and, consequently, long diffusion paths for the dissolved biocides (i.e. low release rates). On the other hand, very fast polishing paints will be eroded away after short immersion times, which involves the need for frequent repainting. In order to measure the degree of polishing, it is necessary to have a reference point indicating the original dry film thickness (DFT) of the paint. For that, a sea water-insoluble acrylic paint is usually applied on selected parts of the AF paint film. At certain time intervals, a paint sample is removed and subsequently analysed with an optical microscope. Prior to that, the paints must be mounted on paraffin and sliced by means of a microtome in order to attain a smooth cross section surface for analysis. This optical inspection technique provides both the degree of polishing and the thickness of the pigment depleted layer or leached layer (Figure 18).

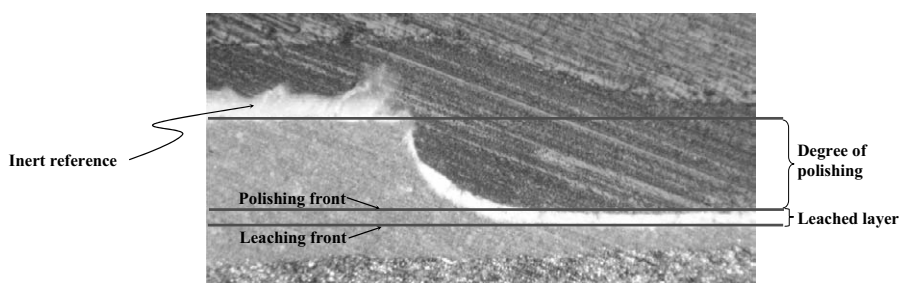


Figure 18: Cross section of an exposed AF paint analysed by an optical microscope (e.g. x200). Schematic illustrations of the different performance parameters obtained from this analysis. (Yebra *et al.*, 2005b).

7.5.8.2 Scanning electron microscopy coupled with energy-dispersive X-ray analysis (SEM-EDX)

The activity of chemically active AF paints usually relies on the reactivity of organometallic compounds (e.g. TBT-, Zn-, Si, Cu- acrylates and Zn-resinates) and inorganic pigments (i.e. Cu_2O). In spite of this, scanning electron microscopy coupled with energy dispersive X-ray detectors (SEM-EDX) has not been used extensively to characterise such reactions. Bishop and Silva

(1969) and Abd El-Malek *et al.* (1987) used SEM analysis to study the surface morphology of exposed AF paints as a function of binder composition and the particle volume concentration, particle size and shape of Cu_2O pigments. Kuo *et al.* (1999) used SEM to visually demonstrate the self-polishing phenomena of surface-fragmenting, self-polishing, antifouling coatings. However, the most interesting application of SEM-EDX to study AF paints was first performed by Kiil *et al.* (2001) and repeated later on by Yebra *et al.* (2005b), see Figure 19. In these two studies, cross sections of exposed AF paints (TBT-SPC and tin-free respectively) were analysed by SEM-EDX in order to study the distribution of the compounds involved in the key mechanisms responsible for the paint performance along the active paint region (i.e. the leached layer). Such studies were subsequently used to set a condition for surface polishing which allowed the mathematical modelling of erosion of chemically-active AF paints. In Yebra *et al.* (2005b), SEM-EDX is also used to assess the possibility of settling and heterogeneous distribution of pigment particles along the dry film.

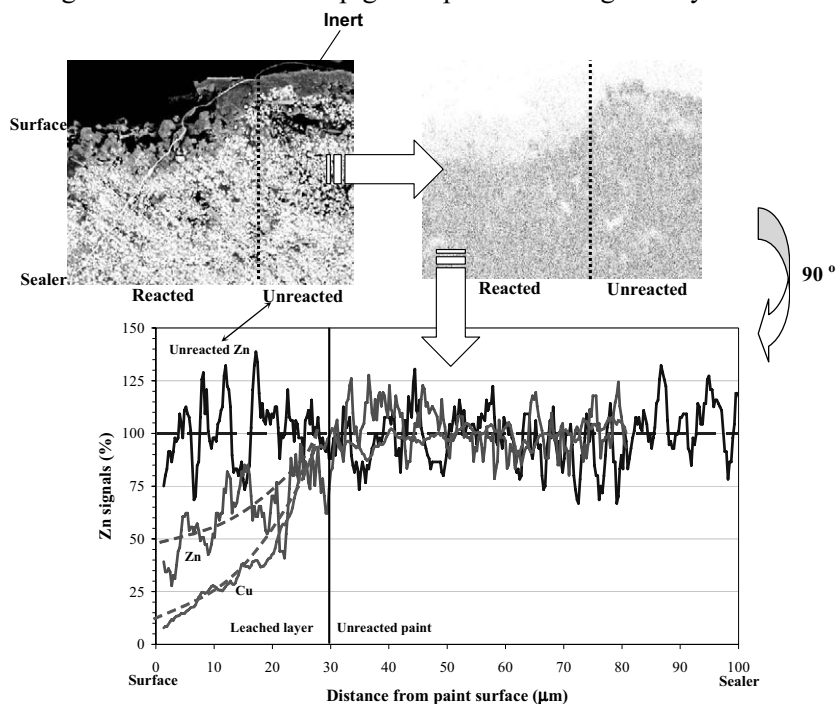


Figure 19: SEM picture of a cross section of an exposed antifouling paint based on ZnR and Cu_2O (upper left picture) and its corresponding EDX analysis showing the Cu signals as dots (upper right picture).

In Fig. 19, the intensity of the Zn (not shown) and Cu signal is processed by means of ImagePro, showing a distinct gradient from the unreacted paint to the paint surface (bottom). Under the inert paint, the Zn profile is constant and taken as reference (blue lines). The Zn profile in the leached layer (red lines) shows a relative residual Zn value at the paint surface of around 45% of that in the unreacted paint film. The Cu profile (green lines) shows approximately the extent of the leached layer. The reason for the larger fluctuations in the Zn signal is a much lower concentration compared to Cu.

7.6 Mathematical paint models

7.6.1 Simulation Tools

Testing and development of chemically active antifouling paints have for many years been based on an almost empirical approach. Optimisation and evaluation of novel and existing products are for example frequently conducted by means of systematic paint rotary tests in the laboratory or at sea sites. Other methods include raft and ship patch testing, the use of bilge and keel panels, leaching rate measurements, and bioassay testing. Various attempts have been conducted over the past 35 years to provide a theoretical basis for the polishing and leaching behaviour of different types of antifouling paints (Kiil *et al.*, 2003). Early attempts cover insoluble matrix paints whereas more recent simulation tools address the more advanced self-polishing paint types. In this section, some of the results produced with the latter models will be reviewed. A fundamental model of the paint behaviour can be used to give reliable estimates of the paint life time at given seawater conditions and paint composition, as well as to suggest ways for optimisation of the paint with respect to biocide release rates. Furthermore, an insight into the release mechanism of existing paints may help to identify the properties that new efficient and environmentally friendly alternatives should possess. Finally, product innovation is facilitated with a profound understanding of how an antifouling paint works.

7.6.2 Simulations of the effect of paint formulation parameters on the antifouling paint behaviour

In Kiil *et al.* (2002a), the effects of seawater parameters and paint formulation parameters on the paint behaviour are simulated and discussed. As an example of the use of the mathematical model, the effect of Cu₂O particle size is reviewed here. All present self-polishing antifouling paints use the soluble

pigment Cu_2O as one of the main biocides. In Figure 20 is shown how the polishing and leaching behaviour of the paint is influenced by particle size (i.e. spherical particle diameter) of a monodisperse PSD.

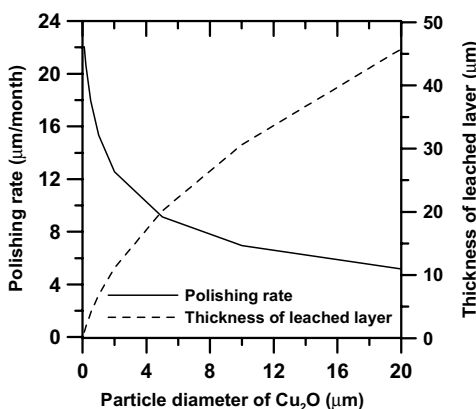


Figure 20: Effect of Cu_2O particle size of a monodisperse PSD on the polishing rate and the stable thickness of the leached layer of a TBT-based paint with a pigment volume concentration of 40 % (solvent-free basis and no inert pigments). From Kiil *et al.* (2002a). With permission of Trans IChemE.

Here, it should be mentioned that the use of a monodisperse distribution in Fig. 20 is not a limitation of the model, but simply a way of presenting simulation results in a comprehensible form. It can be seen in the figure that changing the particle size from 10 to 0.1 μm increases the rate of polishing from 6.9 to 22.1 $\mu\text{m}/\text{month}$. However, reducing the particle size from 20 to 10 μm only changes the polishing rate from 5.2 to 6.9 $\mu\text{m}/\text{month}$. Thus, Cu_2O particle size does not appear to be a key parameter in the formulation of paints with certain controlled release rates of biocides, though very small particles appear to increase the polishing rate significantly. The stable thickness of the leached layer is quite sensitive to particle size (Figure 20). When lowering the particle size from 20 to 0.1 μm , the leached layer thickness decreases from about 46 μm to about 1 μm .

7.6.3 Dynamic Simulations of Paint Behaviour

The mathematical model underlying the simulations is described in detail in Kiil *et al.* (2001) and used for performing dynamic simulations in Kiil *et al.* (2002b). The physical process is described in the earlier section on working mechanisms of antifouling paints. Here, as an example the effect of temperature changes on

a self-polishing antifouling paint is simulated and discussed. The temperature of the world oceans vary between -2 and 30 °C. Consequently, ocean-going ships can experience fast temperature changes upon sailing from cold areas to tropical regions in a matter of weeks. In Fig. 21, it is shown how the rate of movement of the polymer and pigment fronts varies with step changes in temperature (Kiil *et al.*, 2002b).

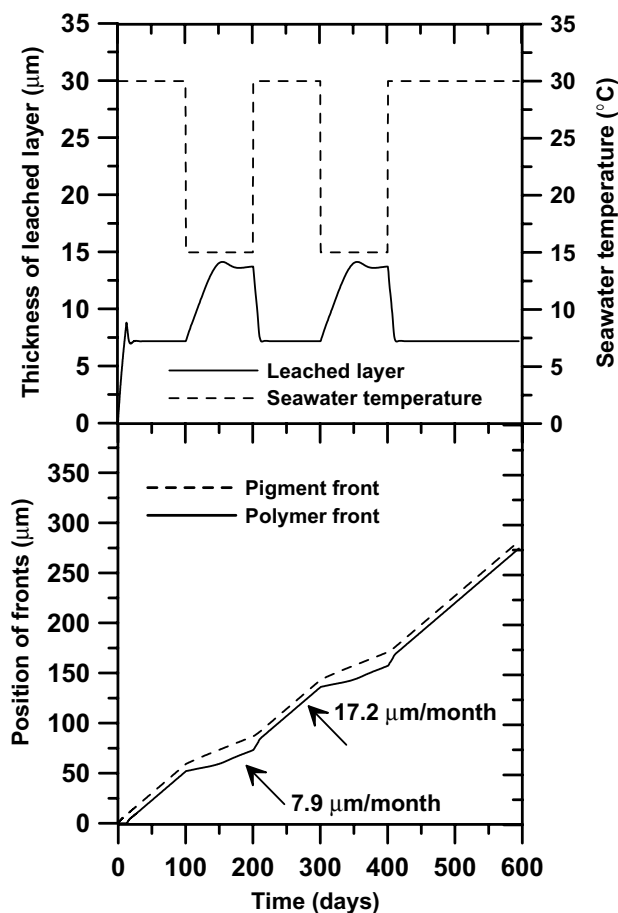


Figure 21: Dynamic simulations showing the effects of step changes in seawater temperature on the rate of movement of the pigment and polymer fronts, as well as the thickness of the leached layer. Two points of stable polishing rates are indicated with arrows. From Kiil *et al.* (2002b). Reproduced with permission of the American Chemical Society.

The distance between the two moving fronts (i.e. the thickness of the leached layer) is also shown. It is evident that an instant temperature reduction from 30 to 15 °C decreases the rate of polishing and dissolution and causes the thickness of the leached layer to start growing. Two months is the time it takes to reach the maximum leached layer thickness of about 14 µm. The reason why the leached layer grows in size when the temperature is reduced is because the activation energy for the rate of pigment dissolution is smaller than that of the rate of hydrolysis of the binder (Kiil *et al.*, 2001). It should also be noted that it takes about 100 days, following the temperature change, for the leached layer to reach a stable thickness. When performing ship tests this is important because a paint present on a ship that experiences a temperature reduction over a short period of time probably does not reach the stable leached layer thickness, which corresponds to the lower temperature, in the test period. In the figure it can also be seen that a sudden temperature increase from 15 to 30 °C reduces the leached layer thickness from just below 14 to about 7 µm, but this only takes 20-30 days. Thus, the paint behaviour stabilises more rapidly from a temperature increase than from a temperature reduction. This is because reaction rates increase with an increase in temperature. The effect of step changes in temperature on the release rates of Cu^{2+} and TBTCI is shown in Fig. 22.

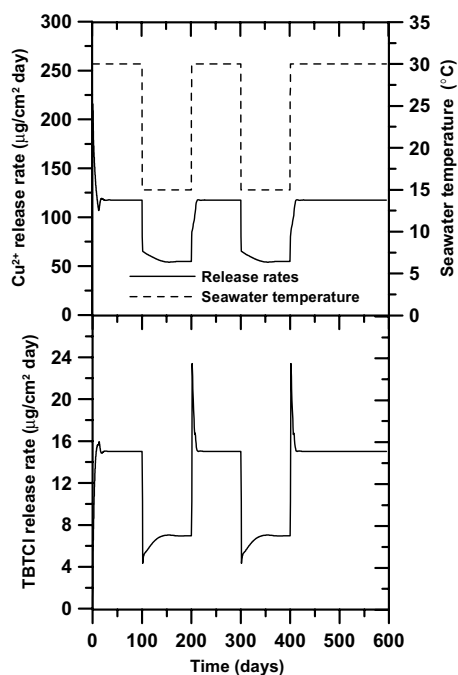


Figure 22: Dynamic simulations showing the effects of step changes in seawater temperature on the release rates of TBTCI (aq) and Cu^{2+} . From Kiil *et al.* (2002b). Reproduced with permission of the American Chemical Society.

The biocide release rates drop instantly to about half their values when the temperature is reduced from 30 to 15 °C. Additionally, the release rates become stable at the new level after about 80 days with most of the changes taking place during the first 50 days. A temperature increase from 15 to 30 °C results in an initial peak in the TBTCI release rate, but it levels off quite rapidly and reaches a stable value after about 30 days. The peak in the TBTCI release rate can be attributed to the reduction of the leached layer thickness when the temperature is increased as discussed in Kiil *et al.* (2002b). However, the Cu^{2+} release rate does not show a peak initially when the temperature is increased. The reason for this is that the Cu^{2+} -ions all originate from Cu_2O dissolution at the pigment front, whereas the hydrolysis reaction takes place in the pores of the entire leached layer.

In Kiil *et al.* (2002b) dynamic simulations of the effect of pH, sailing speed, and salinity on the polishing and leaching rates are shown. To illustrate the usefulness of the model approach, a simulation with a combined change in seawater temperature and sailing speed (i.e. a potential sail service for a large ocean-going ship) is shown in Fig. 23 (Kiil *et al.*, 2002b).

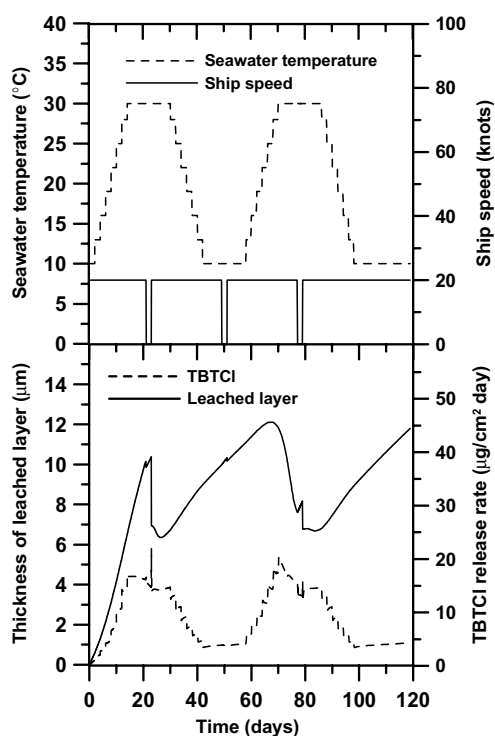


Figure 23: Dynamic simulations showing the effects of seawater temperature and ship speed changes, along an approximated typical sail service, on the release rates of TBTCI (aq) and the thickness of the leached layer. From Kiil *et al.* (2002b). Reproduced with permission of the American Chemical Society.

The effects of dynamic changes in seawater temperature and sailing speed on the thickness of the leached layer and the rate of release of TBTCI can be seen. The sail route shown approximates the conditions a ship sailing between Northern Europe (10 °C) and a tropical region (30 °C) would experience. The ship is assumed to be in port (zero speed on the figure) for two days only in both the tropical and the cold region. It can be seen that the thickness of the leached layer varies between about 6 and 13 μm , depending on the location of the ship. Of more importance is the observation that the release rate of TBTCI varies between about 3 and 22 $\mu\text{g}/(\text{cm}^2\cdot\text{day})$ (disregarding the initial 10 days) and that of Cu^{2+} (not shown) between about 36 and 126 $\mu\text{g}/(\text{cm}^2\cdot\text{day})$. Thus, according to the model the biocide release rates vary by a factor of 3-7 along the sail route. It is an advantage, however, that the release rates are at maximum in the tropical areas, where the fouling is most severe. Details of the paint behaviour in Fig. 23 are provided in Kiil *et al.* (2002b).

7.6.4 Seawater-soluble pigments and their potential use in antifouling paints

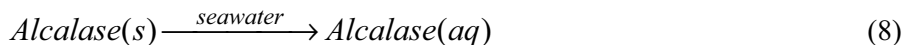
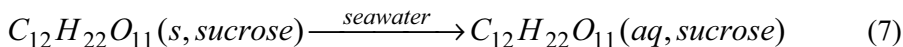
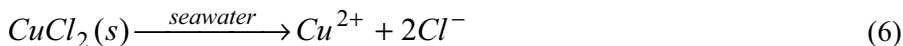
It is evident, when reading through the open literature, that a large number of active components are presently being considered for use in self-polishing antifouling paints (see review by Rittschof, 2001). These include “natural” compounds such as terpenoids, steroids, fatty acids, and aminoacids, heterocyclics, and various organic biocides such as Copper Omadine and Zineb. However, the use of “natural” antifoulants in a functional coating is a technological, financial, temporal and regulatory challenge (Rittschof, 2001). In Kiil *et al.* (2002c) the mathematical model described above was modified to enable a simulation-based exploration and screening of seawater-soluble pigments for their potential use in a self-polishing antifouling paint. Here, a selected example from that work is discussed. The reader is referred to the original reference for more details.

"Pigment", in the present context, refers to relevant seawater-soluble particulate solids. The reaction that takes place at the dissolving pigment front (see Fig. 24) can be written, in general terms, as



The pigment, $P(s)$, can, in principle, be any seawater-soluble particulate solid that is being considered for a potential use in a self-polishing antifouling paint. Salts, sugars, and proteins (enzymes, peptides, or hormones) are obvious examples. It should be noted that the pigment can also represent a seawater-

soluble solid carrier material with any of the aforementioned active ingredients dispersed within the pigment or a coated particle with active material inside. The dissolved pigment species, $S(aq)$, can represent a complex (such as $CuCl_2^-$ in the case of Cu_2O dissolution), an ion (for instance Cu^{2+} if the pigment is $CuCl_2$) or just a physically seawater dissolved species such as sucrose. a and b represent stoichiometric coefficients of a given reaction. In summary, selected examples (perhaps not all of practical importance) are:



According to Schneider and Allerman (2001), Alcalase is the name of an enzyme that might be used to hydrolyse e.g. barnacle proteins. Less than 5 wt% (solvent-free basis) enzyme is used in an antifouling paint (Schneider and Allerman, 2001) and so a seawater-soluble carrier material should probably be used with the enzyme.

For the purpose of a general simulation, the model was expressed in such a way that the following two dimensionless parameters could be varied by the user

$$\alpha = \frac{M_p C_s a}{\rho_p b}$$

$$\beta = \frac{D_{e,S}}{D_{L,OH^-}^o}$$

The parameter α , represents a dimensionless seawater solubility of a given pigment. If the pigment, $P(s)$ of reaction (1), represents a carrier material containing dispersed active ingredients then α must be the dimensionless solubility of this multiphase particulate solid system. β represents a dimensionless effective diffusion coefficient of the dissolved pigment species in the leached layer. Thus, by varying α and β it is possible to see how a given seawater-soluble pigment will influence the polishing and leaching behaviour of a self-polishing antifouling paint. The effects of the model parameters α and β on the polishing rate and the stable thickness of the leached layer at 30 °C are shown in Fig. 24. It can be seen that both parameters have a significant influence on the paint behaviour. Increasing α from 10^{-8} to 10^{-6} , while keeping β

constant at 0.04, increases the rate of polishing from 4 to 51 $\mu\text{m}/\text{month}$ and the stable thickness of the leached layer from 2 to 25 μm . Similarly, increasing β from 0.04 to 0.2, while keeping α constant at 10^{-7} , increases the rate of polishing from 15 to 34 $\mu\text{m}/\text{month}$ and the stable thickness of the leached layer from 8 to 17 μm . At the conditions underlying the simulations of Fig. 24, the polishing rate clearly becomes too high at values of α greater than about 10^{-7} ($\beta=0.04$) or $5 \cdot 10^{-7}$ ($\beta=0.008$). A commercial self-polishing antifouling paint should typically polish at a rate of 5–15 $\mu\text{m}/\text{month}$, depending on the seawater temperature, pH, salinity and sailing speed. The usefulness of the simulations in Fig. 24 is that they can be used for an initial evaluation of a given seawater-soluble pigment.

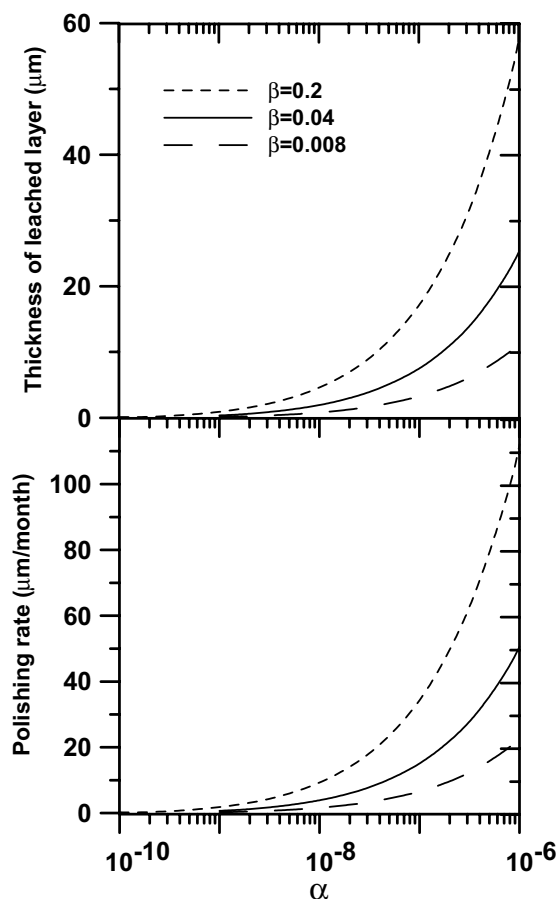


Figure 24 Simulations showing the effects of the model parameters α and β on the polishing rate (at conditions of a stable leached layer thickness) and the stable thickness of the leached layer. $T=30\text{ }^{\circ}\text{C}$. From Kiil *et al.* (2002). Reproduced with permission of Elsevier.

From a calculation of α and β and a reading on the figure, the expected polishing rate and stable leached layer thickness can be estimated. If this exercise suggests a suitable paint behaviour then one may proceed with elaborate rotary experiments. Summarising, the mathematical model represents a simulation tool that enables an accelerated screening of new potential seawater-soluble pigments. This is useful information in the design of novel carrier systems or simply for estimating the rate of leaching of a given active ingredient in particulate form.

7.6.5 Tin-free Systems

The TBT-SPC model was further adapted to describe the sea water behaviour of ablative, rosin-based, tin-free systems in Yebra *et al.* (2005a). Rosin-derivatives are widely used in antifouling systems either as the main controlled-release resin in tin-free coatings or as the means of adjusting the intrinsic hydrophobicity of acrylic-based AF systems (Yebra *et al.*, 2004). Compared to the earlier TBT-SPC mathematical paint model (Kiil *et al.*, 2001), the rosin-based paint model includes a pore enlargement process resulting from the dissolution of sea water soluble resins. Additionally, it incorporates a detailed description of the chemical speciation through the Extended UNIQUAC activity coefficient model and the Cu(I) oxidation reaction. The mathematical model has been used to quantify the differences between the tin-free, rosin-based, model paints and the TBT-SPC ones as regards e.g. their pore morphology, binder reactivity and copper release rate (Figure 25). Significantly higher copper leaching rates compared to the TBT-SPC case, resulting from non-tortuous pores and an increased binder hydrophilicity, are reported. Regarding the polishing process, the model paints tested seem to reach a maximum binder conversion value shortly after immersion. The magnitude of such a maximum conversion appears to be linked to the initial content of insoluble paint ingredients. Hence, the physical erosion of the porous, Cu₂O-depleted binder surface, consisting of the insoluble binder components and a residual amount of sea water soluble resins, is hypothesised to determine the polishing rate throughout most of the paint lifetime. In Yebra (2005), it is demonstrated how the use of a highly hydrophobic, yet self-polishing, binder resin is capable of correcting the copper leaching rate of rosin-based products to match that of TBT-SPCs. Precipitation of Cu²⁺ salts in the leached layer is found to be thermodynamically favourable in paints with a high copper leaching rate developing thick leached layers (i.e. low polishing rates).

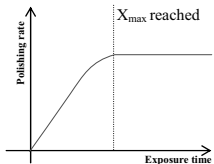
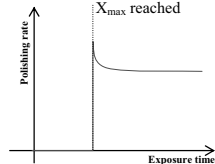
	Ablative Rosin-Based	TBT-SPC
Copper leaching	<ul style="list-style-type: none">• Significant sea water penetration beyond the pigment front• Saturation of Cu(I)-species at the pigment front• Purely diffusion-controlled process	<ul style="list-style-type: none">• Negligible sea water penetration beyond the pigment front• Kinetics of Ferry and Carritt (1946) apply• Chemical reaction and diffusion determine the leaching rate
Pore morphology	<ul style="list-style-type: none">• The pores grow in size with exposure time• Low tortuosity factors• Low pore surface area per total paint volume• Few “bottle-neck” structures	<ul style="list-style-type: none">• The pore size remains largely unchanged• Higher tortuosity factors $\tau=1/\epsilon$• Large pore surface area per total paint volume• “Bottle-necks” formed
Binder reaction	<ul style="list-style-type: none">• High mass loss rates• <i>A priori</i>, the exposed binder surface can be renewed during exposure• The release of Cu^{2+} might influence the binder reaction rate• The reaction seems to be progressively hindered as the conversion increases• Difficulty in reaching 100% conversion	<ul style="list-style-type: none">• Low mass loss rates• The exposed binder surface is not renewed during exposure• Only the pH and Cl^- concentration have been reported to affect the hydrolysis rate• High conversion values may be attained (i.e. the TBT groups beyond the pore walls can be attacked by sea water)
Polishing assumptions (constant exposure conditions)		

Figure 25: Schematic summary of the assumptions which are believed to describe the behaviour of these two dissimilar AF paint systems (Yebra *et al.*, 2005a). The assumptions from the TBT-SPC AF paint system are extracted from Kiil *et al.* (2001)

7.6.6 Experimental Model Inputs

Investigations such as those by Ferry and Carritt (1946) and Hong-Xi *et al.* (1998) on the dissolution rate of Cu_2O particles and the hydrolysis of TBT-MMA polymers can be used as inputs to mathematical AF paint models (Kiil *et al.*, 2001). In the past few years, the study performed by Kiil *et al.* (2001) has encouraged new experimental studies focused on characterising the main processes responsible for the AF sea water behaviour. The core processes to be quantified are (Yebra *et al.*, 2005c):

- Identification of the reaction mechanisms of the multicomponent resin of interest: e.g. the reaction mechanisms of the sea water sensitive multicomponent binder of interest: e.g. possibility of side and reverse reactions, analysis of reaction products and reactants.

- The resin reaction rate at different sea water conditions (e.g. temperature, pH) and paint variables (e.g. retardants, additives).
- The extent to which (i.e. degree of conversion, X_{\max}) the active resin must have reacted at the paint surface to be polished by the moving sea water (influence of insoluble paint components (e.g. TiO_2), sailing speed, paint porosity, etc.).
- The relation between the resin reaction and the booster biocide release process: e.g. water penetration, diffusion through the binder phase
- The dissolution rate and mechanism of dissolution for the soluble pigment particles. Related to that, the characteristics of the porous layer subsequently formed and its influence on the diffusion of species in and out of the paint.
- The chemical speciation and transport of the dissolved species involved in the activity of an AF paint.

The two first points were addressed in Yebra *et al.* (2005c). In such a study, the sea water reaction of a Zn derivative of a refined rosin compound was studied by flame atomic absorption spectrometry (FAAS), Fourier-Transform Infrared spectrometry (FT-IR), SEM-EDX and gravimetric analysis. The hypothesised reaction mechanisms are schematised in Figure 26, the reaction rate at 25 °C, pH 8.2 being about $0.70 \mu\text{g Zn}^{2+} \cdot \text{cm}^{-2} \cdot \text{day}^{-1}$. The sea water temperature and pH were the only parameters influencing the Zn^{2+} release rate, which was found to be virtually irreversible and independent of the Cl^- concentration. Compared to the TBT-SPC binder reaction, a large mass loss rate upon sea water exposure is found to characterise this material, especially if hydrophilic plasticizing resins are used to alleviate its intrinsic brittleness.

Regarding the issue number 3, and following the experimental procedure developed by Kiil *et al.* (2001), Yebra *et al.* (2005b) analysed a number of exposed tin-free AF paints by SEM-EDX in the search for the degree of conversion of the reaction studied by Yebra *et al.* (2005c) at the paint surface during the constant-polishing regime (see X_{\max} definition earlier). The presence of TiO_2 pigments in some of the tin-free paint samples could be successfully used to account for the hiding effect exerted by large amounts of Cu_2O in the unreacted paint film. When several samples of the same paint exposed for different times were analysed, X_{\max} values with an excellent repeatability was obtained (Figure 27).

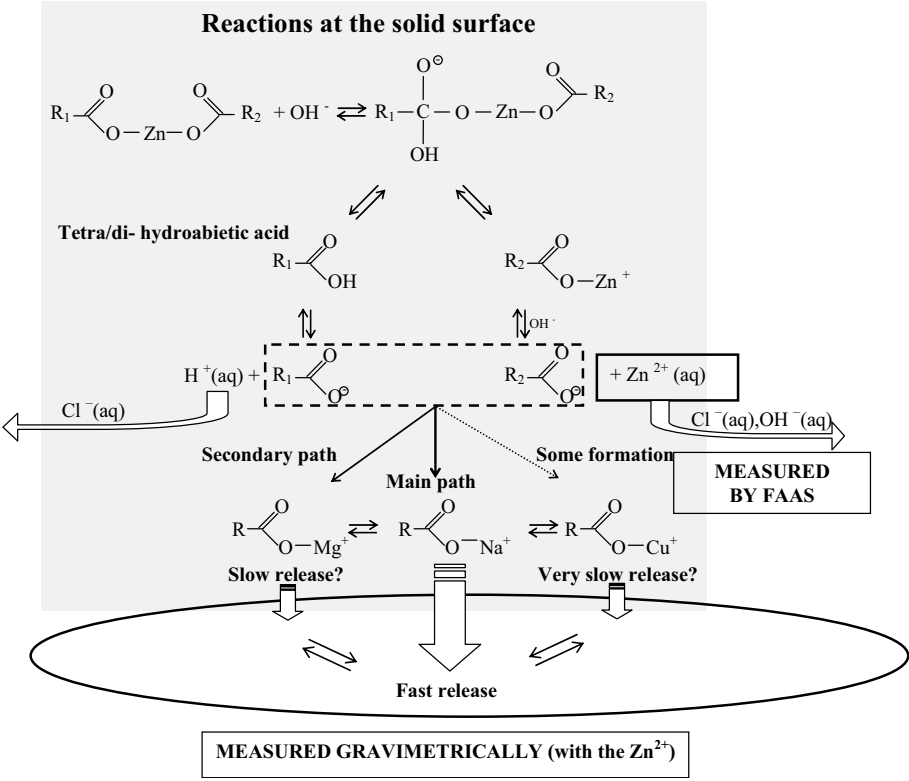


Figure 26: Hypothesised ZnR reactions upon immersion according to the experimental information gathered by Yebra *et al.* (2005c).

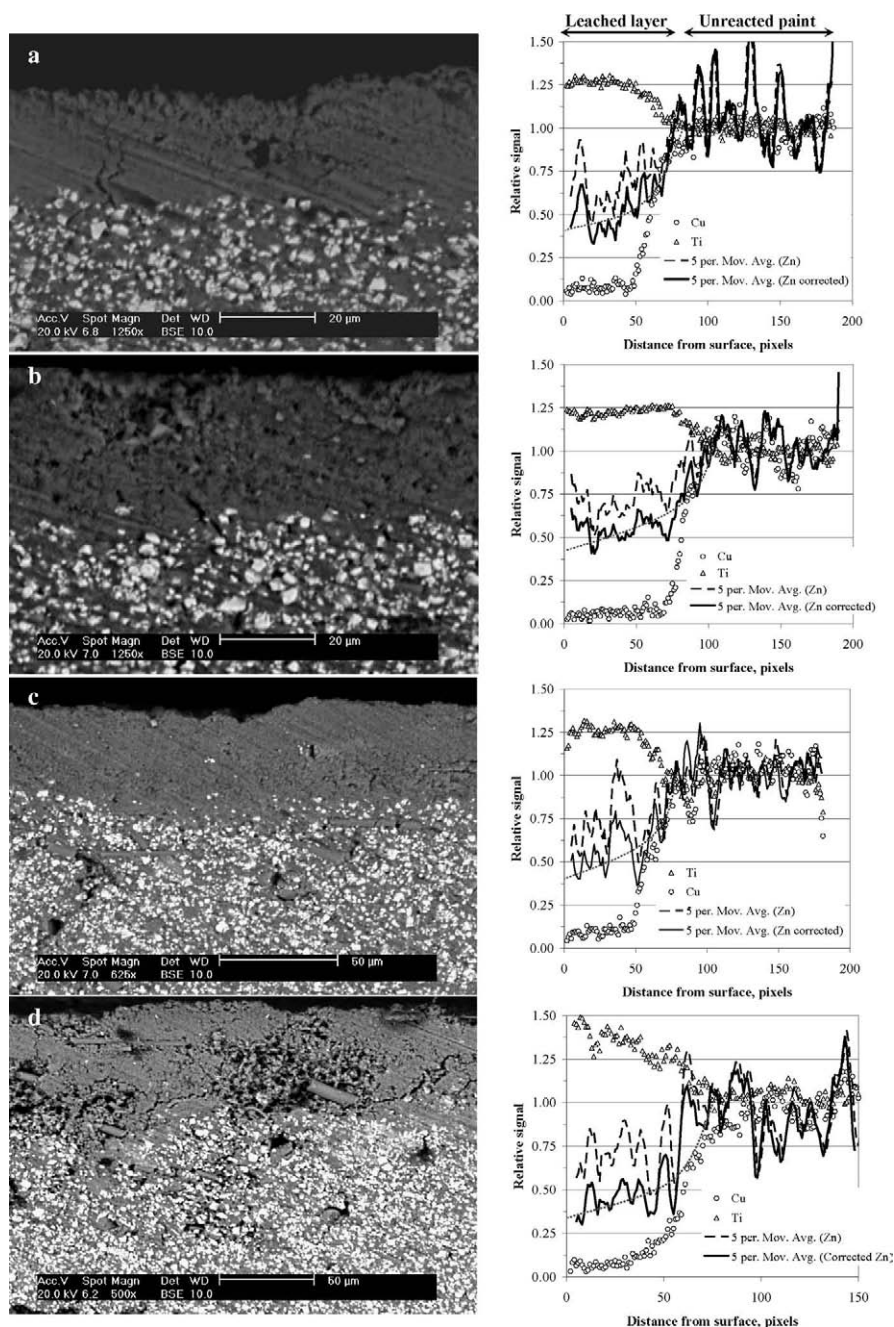


Figure 27: SEM pictures (left) and EDX analysis results (right) of TiO_2 -containing AF model paint formulations exposed to sea water (20 knots) for a) 3

weeks, b) 6 weeks, c) 9 weeks and d) 14 weeks. The value “0” in the x-axis on the right-hand plots corresponds to the paint surface in the SEM pictures (Yebra *et al.* 2005b)

Finally, the determination of the dissolution rate of ZnO (i.e. a sea water soluble pigment) both from pure ultra-smooth monocrystalline ZnO substrates ($\{001\}$ surface) and pellets obtained by sintering technical grade ZnO pigment particles was addressed by Yebra (2005d). The dissolution rates obtained from inductively coupled plasma-mass spectrometry (ICP-MS) analysis were 17.3 ± 3.7 and 55.6 ± 5.6 $\mu\text{g Zn}/(\text{cm}^2 \cdot \text{day})$ respectively. Such a divergence was attributed to the larger exposed surface area (presumably due to higher surface roughness and porosity) and the larger number of defects in the lattice structure which are expected in the pellets. Nevertheless, when ZnO pigments were incorporated into rosin-based binders, the dissolution rate observed was much higher than that obtained from the pellets. As for the Cu_2O pigments, the hydrophilicity of the binder was hypothesised to be responsible for such a phenomenon. A modified leaching test procedure is suggested in the same study, which takes into consideration the pigment-binder interaction. It must be pointed out that the large salt content in the sea water samples leads to somewhat uncertain ICP-MS analytical results due to potential salt deposition at the interface between the ICP and the MS components.

7.7 Approval of Paint Products

7.7.1 AF Paint Registration/regulation Schemes

Due to antifouling paints being chemical preparations they are governed by global, regional and local types of legislation (Pereira, 2003). AF paints are, in most countries, regulated/registered under pesticide laws. Due to the mode of action of the paint, where a biocide is released from the surface, the paint is defined as a biocidal product. An increasing number of countries require approval of antifouling biocides and an authorisation of the products containing them before the paints may be marketed and used. The approval is based on an assessment determining whether the risk towards humans and the environment during the use of the products on both commercial vessels, pleasure crafts, and aquaculture nets is adequately controlled.

7.7.2 Regional and Local Schemes

The most extensive registration scheme for AF products is found in the EU. Biocidal products including AF paints are regulated under The Biocidal Products Directive 'BPD' (EU, 1998a). The aim is to ensure a high level of protection of humans and the environment. Another aim is to harmonise the registration procedures in all 25 member states. During this transitional phase (until 2010) member states' national regulatory schemes, if any, are still in force. Therefore, the European AF legislation as of 2005 represents a spectrum of very extensive legislation to no legislation at all. At present, until the end of the BPD transition period, local registration schemes in European are found in Finland, Sweden, UK, The Netherlands, Belgium, Malta, and Switzerland and schemes with a notification procedures to the local authorities are found in a number of other European countries.

Under the BPD, the biocidal substances are evaluated centrally by the EU Commission. The evaluation is based upon a very extensive data package submitted by the biocide substance manufacturer including a risk assessment of the use of the biocide in AF products. The outcome of the evaluation by the Commission is to decide whether the biocide is prone to be included in a positive list, also termed Annex I, or not.

Upon inclusion onto Annex I, authorisation of AF products containing approved biocidal substances is applied for at member state level. The granted authorisation is based upon a very extensive data package on the AF product submitted by the paint manufacturer. The AF product data package includes data such as physical/chemical properties, toxicological studies, efficacy data, environmental emissions data during application, service time, and maintenance and repair, human exposure data, classification and labelling according to EU laws, and a conclusive risk assessment to determine whether the risk towards humans and environment is adequately controlled.

Authorisations are mutually recognised between member states, but an approval procedure exists in all member states.

In US, AF products need a registration both at federal and at state level. Registration/regulation of AF paints is governed by the Federal Insecticide, Fungicide, and Rodenticide Act 'FIFRA' (US, 2004) and administered by US Environmental Protection Agency. Extensive data packages need to be submitted by the biocide producers and the paint manufacturers. The decision for approval of products is based upon a risk benefit balance evaluation process.

In Australia registration of AF products is governed by a number of Acts, which are administered by Australian Pesticides and Veterinary Medicines Authority (APVMA). The products are registered on a Federal level and control of use of the registered products is performed on a state level.

Japan, South Korea and China, today the countries with the most extensive new ship building industry, have not yet implemented registration schemes for AF products but legislative initiatives are on the way and the coming into force of legislation analogous with e.g. the European BPD is envisaged within near future.

7.7.3 Global Antifouling Paint Legislation

In October 2001, the UN International Maritime Organization (IMO) adopted the International Anti-Fouling Systems Convention (IMO, 2001). According to the convention, application of TBT-based AF paints is banned from 1 Jan 2003. Use of TBT-based AF paint is banned from 1 Jan 2008.

The Convention also includes a methodology to regulate AF systems by evaluating AF biocides based upon data submission by the biocide producers. However, TBT is the first substance on the list of banned substances. The required number of member countries has not yet ratified the convention. However, EU has implemented a directive banning sale and application of TBT-based paints in EU (EU, 2002). As ratification by each of the 25 EU member states is a long process the EU has implemented a Regulation, which in principle implements the IMO convention into all EU countries. According to this Regulation, EU flagged ships are not allowed to apply TBT based paint after 1 July 2003 and any ships irrespective of their flag are not allowed into any EU port by 1 Jan 2008 if they use TBT based paint.

7.7.4 Other Legislation Covering Paint Products

Patently, the legislation with the most direct impact on AF paints is the Biocidal Products Directive as well as other legislative measures covering the biocidal products specifically. However, as it is shown in the following list, a number of other legislative instruments exists that need to be considered when formulating and marketing AF paints. The list is not exhaustive but is solely covering the most important pieces of European legislation. The trend, however, is that

countries on a global scale are implementing alike legislation which on an overall basis is aligned to equal principles and intentions.

Importantly, the laws mentioned below cover not only paint products but chemical components and preparations in general. For the sake of clarity, paint is used as an example to illustrate the intention of each of the legislations mentioned.

- Dangerous Substance Directive. Gives provisions on how to classify, package and label the individual dangerous substances that goes into the paint product (EU, 1967).
- Dangerous Preparations Directive. Gives provisions on how to classify, package and label the paint product that contains dangerous substances (EU, 1988) (EU, 1999a).
- Chemical agents Directive. Gives provisions on how to assess the risk from the handling of dangerous substances on the workplace in order to protect workers adequately (EU, 1998b).
- Restrictions on Marketing and Use Directive. Sets detailed restrictions and total bans on a number of individual substances, e.g. the use of TBT in paint, the use of cadmium, the use of carcinogenic substances as well as approximately 30 other substance specific measures (EU, 1976).
- Safety Data Sheet Directive. Gives provisions on how and in which format to communicate information on dangerous substances and preparations (EU, 1991).
- The Seveso Directive. Sets provisions for workplaces stocking certain amounts of dangerous substances (EU, 1996).
- The VOC Solvents Directive. Sets fugitive emission limit values for the Volatile Organic Compounds in the paint (EU, 1999b).
- REACH. In 2003 the EU Commission proposed a new chemicals policy – REACH (Registration, Evaluation, and Authorisation of Chemicals). The biocides used in AF products are still registered through the BPD, but the other paint constituents as with all other chemical constituents produced or imported > 1 ton/year on the European market will need to be partly or fully risk assessed under REACH. The legislation is expected to enter into force in 2007 (EU, 2003b).

7.8 Conclusions and Future Solutions

This chapter has provided a concise introduction to the design of antifouling paints. It has been shown how the paint development is driven by both empirical testing and formulation and advanced simulation tools. The research

area is multidisciplinary, involving expertise from chemistry, biology, engineering, and finance.

Several very different product ideas have been and are under development. However, many years of research and testing are still to be expected before “ideal” commercial solutions are available for any type of boat or ship. One of the reasons for this is that the sailing pattern of a navy vessel is very different to that of a large ocean-going bulk carrier, which again differs from that of a pleasure craft. Additionally, the requirements given by environmental legislation severely limit the introduction of new active ingredients and controlling the release of most biocides over a 3-5 years period is not easy.

The most likely outcome seems to be that a range of commercial solutions will be available rather than a single dominating product type such as in the days of the tin-based self-polishing paints.

Acknowledgements

The authors are grateful for contributions from Marianne Pereira, Merete H. Laursen, Claus Ankjærgaard, Neel Winther Hinge, Pere Català and Dr. Santiago Arias (all employed at Hempel A/S).

References

- Abarzua, S., Jakubowsky, S. Biotechnological investigation for the prevention of biofouling. I. Biological and biochemical principles for the prevention of biofouling. *Marine Ecology Progress Series* 123 (1995), 301-312.
- Abd El-Malek, M.M., Mohsen, R.M., Ayoub, M.M.H., New approach to the effect of binder composition on antifouling efficiency using scanning electron microscopy. *JOCCA* 11 (1987), 337-341.
- Anderson, C.D., Hunter, J.E. (2000). Whither Antifoulings after TBT?. NAV2000 Conference Proceedings, Venice, September.
- Anderson, C., Atlar, M., Callow, M., Candries, M., Milne, A., Townsin, R.L. The development of foul-release coatings for seagoing vessels. *Journal of Marine Design and Operations*, December issue (2003), 11-23.
- APVMA. The 7 acts to be found on www.apvma.gov.au.
- Arias, S. Round robin test for antifouling paints. *European Coatings Journal* 03 (1999), 122-128.
- Bertram, V. Past, present and prospects of antifouling methods. 32nd WEGEMT School on Marine Coatings, pp.85-97. Plymouth, UK, 10-14 July (2000).
- Bishop, J.H., Silva, S.R. The examination of the structure of antifouling coatings by scanning electron microscopy. *JOCCA*, 52 (1969): 201-218.

- Berendsen, A. M., Marine painting manual, Graham & Trotman, Kluwer Academic Publishers Group (1989)
- Callow, M.E. Ship fouling: problems and solutions. Chemistry & Industry. Vol. 5 March (1990), 123-127.
- Clare, A.S., Rittschof, D., Gerhart, D.J., Maki, J.S. Molecular approaches to non-toxic antifouling. Invertebrate Reproduction and Development, 22(1-3) (1992), 67-76.
- EU (1967) Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. Official Journal P 196 , 16/08/1967 P. 0001 - 0098
- EU (1976) Council Directive 76/769/EEC of 27 July 1976 on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and preparations. Official Journal L 262 , 27/09/1976 P. 0201 - 0203
- EU (1988) Council Directive 88/379/EEC of 7 June 1988 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. Official Journal L 187 , 16/07/1988 P. 0014 - 0030
- EU (1991) Commission Directive 91/155/EEC of 5 March 1991 defining and laying down the detailed arrangements for the system of specific information relating to dangerous preparations in implementation of Article 10 of Directive 88/379/EEC. Official Journal L 076 , 22/03/1991 P. 0035 - 0041
- EU (1996) Council Directive 96/82/EC of 9 December 1996 on the control of major-accident hazards involving dangerous substances. Official Journal L 010 , 14/01/1997 P. 0013 - 0033
- EU (1998a) Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market. Official Journal No. L 123, 24/4/1998 P. 0001 -0063..
- EU (1998b) Council Directive 98/24/EC of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) Official Journal L 131 , 05/05/1998 P. 0011 - 0023
- EU (1999a) Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations. Official Journal L 200 , 30/07/1999 P. 0001 - 0068
- EU (1999b) Council Directive 1999/13/EC of 11 March 1999 on the limitation of emissions of volatile organic compounds due to the use of organic solvents in certain activities and installations. Official Journal L 085 , 29/03/1999 P. 0001 - 0022
- EU (2002) Commission Directive 2002/62/EC of 9 July 2002 adapting to technical progress for the ninth time Annex 1 to Council Directive 76/769/EEC. Official Journal No. L 183, 12/7/2002 P.0058 - 0059.

- EU (2003a) Regulation (EC) No 782/2003 of the European Parliament and of the Council of 14 April 2003 on the prohibition of organotin compounds on ships. Official Journal No. L 115, 9/5/2003 P. 0001 – 0011.
- EU (2003b) Proposal for a Regulation of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (Reach), establishing a European Chemicals Agency and amending Directive 1999/45/EC and Regulation (EC) {on Persistent Organic Pollutants} {SEC(2003 1171)/* COM/2003/0644 final - COD 2003/0256 */
- Ferry, J.D., Carritt, D.E. Action of Antifouling Paints. Solubility and Rate of Solution of Cuprous oxide in Seawater. *Industrial and Engineering Chemistry*, 38 (6) (1946), 612-617
- Godwin, L. S., (2003), Hull fouling of maritime vessels as a pathway for marine species invasions to the Hawaiian Islands Biofouling, Vol. 19(supplement), 37-43.
- Katranitsas, A., Castritsi-Catharios, J., Persoone, G. The effects of copper-based antifouling paint on mortality and enzymatic activity of a non-target marine organism. *Marine Pollution Bulletin*, 46 (2003), 1491-1494
- Kiil, S., Dam-Johansen, K., Weinell, C.E., Pedersen, M.S., Santiago Arias Codolar (2003), Estimation of Polishing and Leaching Behaviour of Antifouling Paints: a Literature Review Biofouling, Vol. 19(supplement), 37-43.
- Kiil, S., Weinell, C.E., Pedersen, M.S., Dam-Johansen, K. (2002a) Mathematical Modelling of a Selfpolishing Antifouling Paint Exposed to Seawater - A Parameter Study, *Chem. Eng. Res. Des.*, **80** (A1), pp. 45-53.
- Kiil, S. Dam-Johansen, K., Weinell, C.E., Pedersen, M.S., Santiago Arias Codolar (2002b) Dynamic Simulations of a Selfpolishing Antifouling Paint Exposed to Seawater, *J. Coat. Technol.*, **74**(929), 45-54.
- Kiil, S. Dam-Johansen, K., Weinell, C.E., Pedersen, M.S., (2002c) Seawater-soluble pigments and their potential use in self-polishing antifouling paints: simulation-based screening tool, *Prog. Org. Coat.*, **45**, 423-434.
- Kiil, S., Weinell, C.E., Pedersen, M.S., Dam-Johansen, K. Analysis of Self-Polishing Antifouling Paints Using Rotary Experiments and Mathematical Modelling. *Ind. Eng. Chem. Res.* 40(2001), 3906-3920.
- Kuo, P.L., Chuang, T.F., Wang, H.L. Surface-fragmenting, self-polishing, tin-free antifouling coatings. *Journal of Coatings Technology* 71(893) (1999): 77-83
- Minchin, D. and S. Gollash (2003), Fouling and Ship's hulls: how changing circumstances and spawning events may result in the spread of exotic species Biofouling, Vol. 19(supplement), 37-43.
- Haslbeck, E.G., Holm, E.R. Round robin test for measuring copper release rates from antifouling coatings. In preparation for publication in the *European Coatings Journal* 2005.
- Holm E.R., Schultz M.P., Haslbeck E.G., Talbott W.J., Field A.J. Evaluation of hydrodynamic drag on experimental fouling-release surfaces, using rotating disks. *Biofouling* 20(4-5) (2004): 219-226
- Hong-xi, C., Mei-ying, Y., Huai-min, G., Jing-hao, G. Studies on the hydrolysis of the organotin polymers. I. Hydrolytic rates of poly(tributyltin

- methacrylate) and poly(tributyltin methacrylate-co-methyl methacrylate). Fujian Shifan Daxue Xuebao, 4, (2) (1988)., 61-8X. In Chinese.
- IMO (2001). International Convention on the Control of Harmful Anti-Fouling Systems on Ships. AFS/CONF/26.
- Lambourne, R., Strivens, T.A. (eds.) Paint and surface coatings – theory and practise, 2nd ed., 1999.
- Marson, F. Anti-Fouling Paints I. Theoretical approach to leaching of soluble pigments from insoluble paint vehicles. J. Appl. Chem. 19 (1969), 93-99.
- Omae, I. Organotin antifouling paints and their alternatives. Applied Organometallic Chemistry, 17 (2003), 81-105.
- Pereira, M.B. Environmental regulations challenge paint industry. BIMCO Bulletin, 98(1) (2003), 34-37
- Rittschof, D. Natural Product Antifoulants and Coatings Development in: J.B. McClintock, B.J. Baker (Eds.), Marine Chemical Ecology, CRC Press, Boca Raton FLA, 2001, 543-557
- Swain, G. Biofouling control: a critical component of drag reduction. International Symposium on Sea water Drag Reduction, The Naval Undersea Warfare Center, Newport, 155-161 (1998).
- Schultz, M.P. Frictional Resistance of antifouling coating systems. Journal of Fluids Engineering, 126(November) (2004)
- Schneider, I., Allerman, K. Poster presented at workshop "Environmentally Friendly Marine Coatings", Gothenborg, Sweden, 17-19 October (2001).
- US (2004). Federal Insecticide, Fungicide, and Rodenticide Act, 7 u.s.c. s/s 135 et seq. (1972). www.epa.gov/epahome/laws.htm.
- Valkirs, A.O., Seligman, P.F., Haslbeck, E., Caso, J.S. Measurement of copper release rates from antifouling paint under laboratory and in situ conditions: implications for loading estimation to marine water bodies. Marine Pollution Bulletin, 46 (6) (2003): 763-779.
- Vallée-Rehel, K., Langlois, V., Guérin, P. Contribution of pedant ester group hydrolysis to the erosion of acrylic polymers in binders aimed at organotin-free antifouling paints. Journal of Environmental Polymer Degradation, 6(4) (1998b), 175-186
- Voulvoulis, N., Scrimshaw, M.D., Lester, J.N. Review-alternative antifouling biocides. Applied Organometallic Chemistry, 13 (1999), 135-143
- Weinell, C. E., Olsen, K.N., Christoffersen, M.W., Kiil, S. (2003) Experimental Study of Drag Resistance Using a Laboratory Scale Rotary Set-up, Biofouling, Vol. 19(supplement), 45-51.
- Weldon, D. G., Failure analysis of paints and coatings, Wiley, 2002.
- WHOI (Woods Hole Oceanographic Institution). Marine fouling and its prevention. U.S. Naval Institute. Annapolis. Ed.: Iselin, C.O.D., 1952
- Yebra, D.M., Kiil, S., Dam-Johansen, K. Antifouling Technology: Past, Present and Future Steps towards Efficient and Environmentally Friendly Antifouling Coatings. Progress in Organic Coatings 50(2) (2004), 75-104
- Yebra, D.M., Kiil, S.Z., Weinell, C.E., Dam-Johansen, K. Mathematical modelling of chemically-active antifouling coatings: accelerated paint design. Submitted for publication to Biofouling (2005a).

- Yebra, D.M., Kiil, S.Z., Weinell, C.E., Dam-Johansen, K. Parametric Study of Tin-Free Antifouling Model Paint Performance Using Rotary Experiments. Submitted for publication to Biofouling (2005b).
- Yebra, D.M., Kiil, S., Dam-Johansen, K., Weinell, C. Reaction rate estimation of controlled-release antifouling paint binders: rosin-based systems. Progress in Organic Coatings 53(4) (2005c), 256-275.
- Yebra, D.M. Efficient and Environmentally-Friendly Antifouling Paints. Ph.D. Thesis, Department of Chemical Engineering, Technical University of Denmark (2005)
- www.imo.org. Accessed March 2005

Chapter 8

Product-centered Process Synthesis and Development: Detergents

Ho-ki Fung,^a Christianto Wibowo,^b Ka M. Ng^a

^a*Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong*

^b*ClearWaterBay Technology, 20311 Valley Blvd. Suite C, Walnut, CA 91789, USA*

8.1 Introduction

Detergent products, including dishwashing liquids, laundry detergents, household cleaners, fabric softeners, soaps, shampoos, and conditioners, constitute a significant portion of the household and personal care markets. The global market for household products, most of which are detergents, was valued at nearly US\$83.3 billion in 2003, 4.1% up from the previous year [1]. In the U.S. alone, the sales of laundry detergents reached US\$3.8 billion in 2001 [2]. Despite slowing growth compared to the previous decade, the industry is far from stagnant. Motivated by environmental concerns, more energy-efficient washing conditions, and higher-order benefits to consumers, intense innovation work is underway on detergent chemicals that are highly biodegradable, compatible, and multi-functional [3].

Contrary to the commodity chemical business, the key to win in the specialty products market does not lie in squeezing out profits by means of economies of scale or process optimization. Rather, it lies in the ability for fast new product launches in order to capture the largest market share as soon as possible. Since superior product quality and performance is what really differentiates one specialty product from another, the product properties need to be adjusted as required by business needs. For example, the ability to manipulate functional chemicals in detergent products such as enzymes and zeolites, as well as backbone chemicals like surfactants, is often the key to success for both the detergent manufacturers and chemical suppliers [3]. This trend has created an urgent need for an efficient and effective product and process development for these products.

For this reason, this article proposes a product-centered approach which applies chemistry and chemical engineering principles to develop the manufacturing process of detergent products with the desirable performance. The products can have different delivery forms such as powder, tablet, spray, gel, unstructured liquid, and structured liquid. A systematic procedure is presented to provide guidelines for easier and faster product and process development, focusing on how to manipulate the detergent chemicals and the processes involved in response to consumer needs. The procedure highlights specific aspects unique to detergents, which were absent in the previously developed procedures for specialty chemicals in general [4-6]. Without loss of generality, the scope of discussion in this article is limited to detergents that clean non-living objects, excluding others that maintain or improve the cleanliness of human beings, which can be roughly classified as personal care products.

8.2 Procedure

The procedure consists of three steps. The first step is to identify all the desired product quality factors or attributes for the new product. Then what follows is the selection of the appropriate product form and microstructure, a stable surfactant system with the right performance based on phase behavior, and the appropriate active ingredients in order to realize those quality factors previously identified. Finally the process flowsheet will be created with the equipment units and process operating conditions determined.

8.2.1 Step 1: Identification of Product Quality Factors

Product quality factors for detergents can be roughly classified as primary and secondary quality factors. Primary quality factors constitute the minimum requirement for a detergent product, and are regarded by consumers as the prerequisites for any product of the same category available in the market. What distinguish the best-sellers from other products are the secondary quality factors, the higher order attributes that delight consumers by satisfying their unmet needs. A list of commonly targeted primary quality factors and secondary quality factors for detergent products is shown in Table 1.

Most detergent manufacturers nowadays have created a basic building block formula to support the primary quality factors. Their R&D efforts are focused on delivering more secondary quality factors where they can derive desirable profits [2]. Hence the list of secondary attributes will keep on expanding with time. It is indeed these value-added benefits that have been driving the growth of the detergent industry [7]. A good example of these active benefits can be the color protection of garments by laundry detergents with the aid of dye-transfer inhibitors or polymers that coat fabric fibers. Other examples include the fabric care and UV protection delivered to garments by laundry detergents empowered

Table 1. Quality factors for detergents.

Primary quality factors
<ul style="list-style-type: none"> • Fast dissolution and fast effect • Convenient for use • Clean effectively and efficiently regardless of cleaning conditions • High product stability • Small size and light weight with minimum packaging
Secondary quality factors
<ul style="list-style-type: none"> • High biodegradability • Desirable foam amount and duration • Color-fastness of objects to be cleaned, especially for laundry detergents
Improved properties of objects to be cleaned, e.g. UV protection for laundered garment
<ul style="list-style-type: none"> • Enhanced consumer health, e.g. skin care rendered by dishwashing liquids

with fiber strengthening polymers and UV absorbers that deposit on garments during wash, and the skin care by dishwashing liquids that contain anti-irritants, skin vitalizing enzymes, vitamin E, or a combination of them.

In the process of realizing product quality factors by changing product formulation, the relevant performance indices have to be determined. The determination process in turn requires experience and technical expertise. For detergent products the performance indices need to be considered include: (1) optimum hydrophilic-lipophilic balance, HLB_{Op} ; (2) critical micelle concentration, CMC ; (3) soil solubilization capacity, S ; (4) Krafft point, T_{krafft} (in the case of ionic surfactants); (5) cloud point, T_{cloud} (in the case of nonionic surfactants); (6) product viscosity, η ; (7) calcium binding capacity of builders; (8) surface tension reduction at critical micelle concentration, Π_{CMC} ; and (9) dissolution time, t_{di} . Most product quality factors are related to either one or several of these performance indices as shown in Table 2.

Based on the indicated relationship, the desired product qualities are linked to the relevant performance indices. Suppose market surveys show consumers prefer detergents with faster dissolution and faster effect. Then an experienced formulator will identify the HLB_{Op} , CMC , and t_{di} as the relevant performance indices to focus on. A higher HLB_{Op} is targeted since a surfactant molecule with a bigger hydrophilic portion will dissolve in water better. For solid detergent, faster dissolution means, of course, a shorter t_{di} . Some quality factors can limit the feasible range of certain performance indices. For example, the intended application of the detergent product and the desired appearance of the surfactant solution dictate the range of HLB_{Op} for the surfactant system (Figure 1).

Table 2. Examples of relationships between quality factors and performance indices.

<div>Performance Indices</div> <div>Quality Factors</div>	Optimum HLB	Critical micelle concentration (CMC)	Soil solubilization capacity	Kraft point (ionic surfactants only)	Cloud point (nonionic surfactants only)	Viscosity	Calcium binding capacity	Surface tension reduction at CMC	Dissolution time	Material and/or structural attributes
<i>Primary quality factors</i>										
Faster dissolution, faster effect	↑	↑							↓	
Higher convenience for use	√									√
More powerful cleaning			↑			↑	↑	↓		
Higher formulation compatibility										√
Higher product stability						↑				
Better performance in cold temperatures and hard water		↑		↓	↑		↑			
Smaller weight/volume and less packaging							↑	↓		
Broader spectrum of targeted soils	√									
<i>Secondary quality factors</i>										
Higher biodegradability										√
More desirable foam amount and duration	√							√		√
Color retaining										√
UV protection/sun fade protection of fabrics (for laundry detergents only)										√
Human skin protection										√
Fewer spots/films after wash										√

↑ = can be achieved by increasing the performance index

↓ = can be achieved by decreasing the performance index

√ = can be achieved by adjusting (increasing or decreasing) the performance index

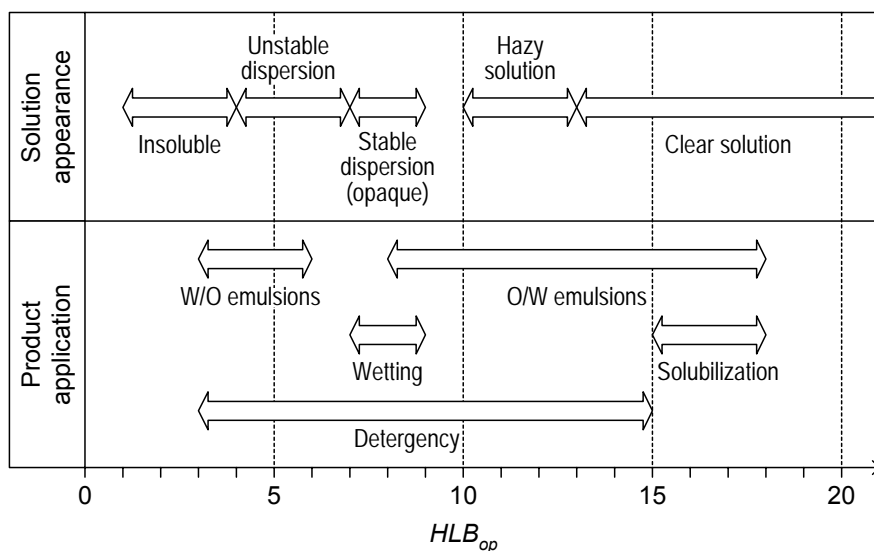


Figure 1. Dependence of surfactant solution appearance and product application on HLB_{op} .

Krafft point (for ionic surfactants) and cloud point (for nonionic surfactants) are both a limit to surfactant solubility. The solubility of ionic surfactants decreases significantly below the Krafft point, since its concentration falls below the *CMC* and individual surfactant molecules cannot form micelles. Therefore, the Krafft point of an ionic surfactant must be below the desired wash temperature for maximum soil removal. In contrast, the solubility of some nonionic surfactants decreases with increasing temperature. Above the cloud point, the surfactant becomes insoluble. Thus, the cloud point of a nonionic surfactant should be 15–30°C above the intended wash temperature [8].

Detergency, or the power of a detergent product to remove soil, depends on the ability of surfactants to lower the interfacial tension between different phases. This can be explained for a typical case where removal of liquid soil is aided by surfactant adsorption onto the soil and substrate surfaces from the cleaning bath (Figure 2) using Young's equation,

$$\gamma_{OB} \cos \theta = \gamma_{SB} - \gamma_{SO} \quad (1)$$

When γ_{SB} is reduced to the extent that $\gamma_{SB} - \gamma_{SO}$ is negative, θ will be larger than 90° and the soil can be completely removed by mechanical agitation in the cleaning bath. Although γ_{SB} and γ_{OB} vary specifically with the use conditions, they can generally be correlated to the surface tension of the product solution [8]. This surface tension is found to decrease with surfactant concentration up to the *CMC*, beyond which there will be no significant surface tension reduction. The surface tension reduction at *CMC*, defined as

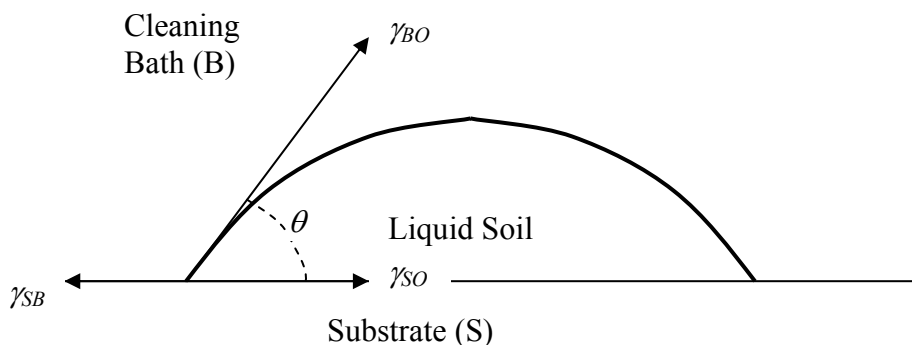


Figure 2. Liquid soil removal from substrate in the presence of surfactants.

$$\Pi_{CMC} = \gamma_0 - \gamma_{CMC} \quad (2)$$

where γ_0 is the surface tension of pure solvent, is therefore a performance index for evaluating the detergency of the product.

Some quality factors, especially secondary ones, depend directly on material or structural attributes of the product. These product quality factors are often arbitrary and can only be qualitatively evaluated by panels of consumers or experts. Convenience for use, product stability, and ability for human skin protection are all examples of these quality factors. Each arbitrary performance index has specific relationships with the material/structural attributes. In such cases, the desirable quality factor can be realized by directly changing the formulation without concerning any of the performance indices. An example can be that to make a laundry detergent product more convenient to use, the product form can be changed from powder to tablet. Another example is that to make a highly biodegradable product, surfactants with less branching should be used.

8.2.2 Step 2: Product Formulation

Performance indices only point out the general direction for the product formulation. For more specific information required in the formulation process, heuristics are usually used to choose the appropriate product form, surfactant system, and additives. This step aims at choosing the appropriate product formulation, namely the product form with the right materials (surfactant system and additives) and product structure, to bring about the quality factors previously mentioned.

Desired changes in the identified performance indices are then translated into changes in material and structural attributes as suggested in Table 3. For example, a higher HLB_{Op} is achieved by using surfactant with a higher weight

Table 3. Relationship between selected performance indices and material or structural attributes.

Performance index	Related material or structural attributes	Relationship
Optimum hydrophilic-lipophilic balance, HLB_{Op}	Weight percentage of hydrophilic group in surfactant molecule, W_{hydro}	$HLB = \frac{W_{hydro}}{5}$
	Weight fraction, w_i (for mixtures)	$HLB = \frac{w_A HLB_A + w_B HLB_B}{w_A + w_B}$
Critical micelle concentration, CMC	Polymeric additive concentration	In general decreases upon addition of polymeric additives
	Optimum HLB	Increases with increasing HLB_{Op}
	Branching of surfactant, br	Increases with increasing br
	Valency of counter-ions, z^*	Decreases with increasing z^*
	Product solution ionic strength, I	Decreases with increasing I (smaller effect for nonionic surfactants)
	pH	System specific (for weak acids and amphoteric)
	Mole fraction, y_i (for mixtures)	$CMC = \frac{1}{\sum_i (y_i / CMC_i)}$ (for ideal mixed micelles of nonionic surfactants)
Soil solubilization capacity, S	Soil polarity	In general, S is higher for polar soils than for non-polar ones
	Critical micelle concentration, CMC	Decreases with increasing CMC
	Lipophilic group volume of surfactant molecule, v	Decreases with increasing v
	Cross-sectional area of hydrophilic group, a_o	Decreases with increasing a_o
	Length of lipophilic group, l_c	Increases with increasing l_c
	Product solution ionic strength, I	Increases with increasing I (for ionic surfactants)
Krafft point, T_{krafft}	Surfactant chain length, l	Increases with increasing l
	Product solution ionic strength, I	Increases with increasing I
	Branching of surfactant, br	Decreases with increasing br
	Valency of counter-ions, z^*	Increases with increasing z^*
Cloud point, T_{cloud}	Surfactant chain length, l	Decreases with increasing l
	Degree of ethoxylation, $\delta_{ethox.}$	Increases with increasing $\delta_{ethox.}$
	Product solution ionic strength, I	Decreases with increasing I

Table 3. Relationship between selected performance indices and material or structural attributes (continued).

Performance index	Related material or structural attributes	Relationship
Viscosity, η	Polymeric additive concentration	In general, increases with addition of polymeric additives
	Branching of surfactant, br	Decreases with increasing br
	Continuous phase viscosity, η_o	$\frac{\eta}{\eta_o} = \eta_{rel} = 1 + 2.5\phi_v$ for $\phi_v < 0.05$
	Dispersed phase viscosity, η_i	$\ln \eta_{rel} = 2.5 \left(\frac{\eta_i + 2/5\eta_o}{\eta_i + \eta_o} \right) (\phi_v + \phi_v^{5/3} + \phi_v^{11/3})$ for $0.05 < \phi_v < 0.4$
	Dispersed phase volume fraction, ϕ_v	
Calcium binding capacity	Builder's hard ions complexation constant, K	Increases with increasing K
	Builder's complexing mechanism	System specific
Surface tension reduction at CMC, Π_{CMC}	Branching of surfactant, br	Increases with increasing br
	Product solution ionic strength, I	Increases with increasing I (for ionic surfactants only)
Dissolution time, t_{di} (for powder)	Particle mass, m	Hixson-Crowell (cube root) equation $t_{di} = \frac{1 - (m/m_o)^{1/3}}{(kS/\rho r_o)}$
	Mass transfer coefficient, k	
	Solubility, S	
	Particle radius, r	
	Density, ρ	
Dissolution time, t_{di} (for tablet)	Tablet mass, m	Order-of-magnitude model derived from Fick's and Darcy's laws [6] $t_{di} = \frac{2m^2}{\pi^2 d_p^2 H^4 D \varepsilon (1 - \varepsilon)^2}$
	Diffusivity, D	
	Grain particle size, d_p	
	Tablet size, H	
	Porosity, ε	

percentage of hydrophilic group, W_{hydro} [9]. Dissolution time can be shortened by having larger diffusivity D for the material, or smaller powder size d_p . Note that some performance indices are interrelated, such as soil solubilization capacity, optimum HLB, and CMC. Therefore, changes in one performance index may affect the other indices.

8.2.2.1 Selection of Product Form

The selection of product form for detergent products covers a wide range of choice, including spray, liquid (unstructured or structured), gel, sachet, powder, and tablet. To a large extent, the choice of product form is a tradeoff between convenience and cost. Liquid form is more convenient than powder or tablet form because of its immediate cleaning action. Also, it does not cake in storage as powder does. However, liquid generally possesses fewer active ingredients than powder of the same volume, hence it is bulkier and requires special

packaging. The intended application is also an important factor. For example, the spray form is unrivaled by other product forms in its ability to eliminate spot and streak issues, which is why glass cleaners are often sold in this form [10]. Table 4 shows the advantages and disadvantages of different product forms, which highlight the tradeoffs and serve as guidelines for selection.

Liquid detergents available in the market can roughly be classified into two categories. Unstructured liquids, which appear translucent, has a large continuous water phase with all active ingredients solubilized in it. Structured liquids are opaque and viscous, and consist of a phase of surfactant lamellars suspended in a continuous water phase [11]. The requirement for phase stability for structured liquids limits the surfactant ratios and often requires the use of electrolytes in high concentration, but the structure allows incorporation of useful but insoluble additives such as zeolite. The water phase in both unstructured and structured liquids is replaceable by non-aqueous liquid, such as in products for cleaning metallic or ceramic surfaces that do not tolerate significant exposure to moisture.

Table 4. Heuristics for product form selection.

<i>Product form</i>	<i>Advantages</i>	<i>Disadvantages</i>
Spray	<ul style="list-style-type: none"> • does not require dilution • suitable for uniform application over a small area (spot cleaning) 	<ul style="list-style-type: none"> • not suitable for heavy duty applications
Unstructured liquid	<ul style="list-style-type: none"> • dissolve rapidly in cold water • does not generate dust • lenient phase stability and viscosity requirements 	<ul style="list-style-type: none"> • tend to be heavy and bulky • can only incorporate soluble ingredients (no insoluble solids)
Structured liquid	<ul style="list-style-type: none"> • dissolve rapidly in cold water • does not generate dust • can accommodate insoluble solids 	<ul style="list-style-type: none"> • tend to be heavy and bulky • strict phase stability and viscosity requirements
Gel	<ul style="list-style-type: none"> • increased dwell time and less runoff compared to liquid form • dissolve faster than solid form • allow suspension of insoluble solids 	<ul style="list-style-type: none"> • require extra processing steps
Sachet	<ul style="list-style-type: none"> • very precise dosage • convenient storage and usage 	<ul style="list-style-type: none"> • stricter processing and packaging requirements compared to liquid/gel
Powder	<ul style="list-style-type: none"> • light and small packaging • lenient solubility requirement for ingredients 	<ul style="list-style-type: none"> • no cleaning action without dissolution • caking problem during storage
Tablet	<ul style="list-style-type: none"> • very precise dosage • convenient storage and usage 	<ul style="list-style-type: none"> • require extra processing steps • prone to breaking and disintegration during processing

8.2.2.2 Selection of Surfactant System

A suitable surfactant system has to be selected next. Table 5 summarizes the general guidelines for choosing surfactants based on the desirable properties. Surfactants to choose from can be anionic, cationic, nonionic, or zwitterionic. Anionics are the best choice if material cost is the key concern. Cationics are more often used for substrate modification (e.g. fabric softening) rather than cleaning, because they possess poor detergency, as their positively charged surface active moieties can adsorb onto and neutralize most solid surfaces (which are usually negatively charged). Nonionics and zwitterionics are compatible with all other types of surfactants and milder to human skin compared to their ionic counterparts, but zwitterionics are insoluble in organic solvents. Several performance indices can be used as guidelines for selecting surfactant system, including optimum Hydrophilic-Lipophilic Balance (HLB_{Op}), detergency, viscosity, soil solubilization capacity, and Krafft point or cloud point.

Table 5. Heuristics for surfactant selection.

<i>Target property</i>	<i>Selection guidelines</i>
Good cleaning power	<ul style="list-style-type: none"> • Use a mixture of surfactants to better match the required HLB_{Op} • Choose surfactants with high detergency, usually in the C10-C16 range
Low environmental impact	<ul style="list-style-type: none"> • Choose surfactants with linear hydrocarbon chains over those with branched chains, since the earlier is more biodegradable
Low cost	<ul style="list-style-type: none"> • Choose from the following most widely used ones: soaps, linear alkylbenzene sulphonates (LABS), alcohol ethoxysulphates (AES), alcohol sulphates (AS), alkane or paraffin sulphonate (SAS), and alcohol ethoxylates (AE)
Long-lasting foam	<ul style="list-style-type: none"> • Use anionic or amphoteric surfactants, or a mixture of the two for high foaming
Mildness to human skin	<ul style="list-style-type: none"> • Use nonionic surfactants, zwitterionic surfactants, or a combination of both with additives that are antiirritants, such as modified proteins or polymers
High solubility	<ul style="list-style-type: none"> • Use surfactants with shorter carbon chains • Choose potassium salt surfactants over their sodium cation counterparts
Resistance to water hardness	<ul style="list-style-type: none"> • Use nonionic surfactants, which are less sensitive to hard water ions than anionics, especially when solubility limitation imposed by the product restricts the use of high builder level
Fabric softening	<ul style="list-style-type: none"> • Use cationic surfactants for their high substantivity on surfaces, especially negatively charged ones and the subsequent surface modification

The target value of HLB_{Op} can be matched by either single surfactant or surfactant mixture, but the latter is in general more effective in stabilizing emulsions [12]. Hence the HLB_{Op} can be achieved by mixing surfactants with the right individual HLB values in the right proportions. Similarly, the targeted CMC value can be achieved using surfactant mixtures. To achieve the desired soil solubilization capacity (S), which measures the capability of a detergent to hold the soils and prevent them from re-depositing on the substrate, a surfactant with an appropriate value of aggregation number (n_{Agg}) should be selected. This number in turns depends on the chemical structure of the surfactant molecule (as represented by v , a_0 , and l_c in Table 3). The targeted Krafft point and cloud point can be met by using surfactants with appropriate chain length, branching, and ethoxylation level (for nonionics).

For liquid detergent, product viscosity is another important performance index. Surfactants will exhibit different phase behavior according to the packing factor, v/a_0l_c , where v is the lipophilic group volume of the surfactant molecule, a_0 is the cross-sectional area of the hydrophilic group, and l_c is the length of the lipophilic group. Since different phases have different viscosity behavior, the selection of surfactant system is restricted by the desirable viscosity behavior. Table 6 summarizes the phase and viscosity behavior of surfactant system with different values of packing factors. It should be noted that the size and shape of the micelles will also change with surfactant concentration and product solution ionic strength.

Surface tension reduction at CMC , Π_{CMC} , increases with branching of surfactant, br and product solution ionic strength, I . Branching of surfactant can in turn be promoted by either moving hydrophilic group from the terminal position to other positions, or having more lipophilic groups attached to the polar head.

8.2.2.3 Selection of Additives

Special attention should be paid to the selection of additives, as they drive the higher-order quality factors that differentiate one product from another. Table 7 summarizes commonly used additives in detergent products along with their

Table 6. Dependence of viscosity behavior on packing factor.

Packing factor	Phase structure	Viscosity
$0 < v/a_0l_c < 0.33$	spherical micelles with polar ends in the outer shell	0-1,000 cP (Newtonian)
$0.33 < v/a_0l_c < 0.5$	cylindrical micelle in hexagonal structure	1,000-100,000 cP (Rheopeptic/thixotropic)
$0.5 < v/a_0l_c < 1$	Lamellar	1,000-50,000 cP (Thixotropic)
$v/a_0l_c > 1$	reversed micelle in non-polar medium	0-1,000 cP (Newtonian)

Table 7. Typical additives used in detergents.

<i>Additive</i>	<i>Desired function</i>	<i>Selection criteria</i>	<i>Examples</i>	<i>Typical amount</i>
Abrasives (DW, HC)	Provide smoothing, scrubbing, or polishing action	Hardness	Calcite	0-55%
			Feldspar	60-90%
			Quartz	-
			Sand	0-15%
Acids (HC)	Neutralize or adjust alkalinity of other ingredients	pH target for the final product	Acetic acid	0.5-10%
			Citric acid	0.5-20%
			Hydrochloric acid	0.5-20%
			Phosphoric acid	0.5-20%
			Sulfuric acid	-
Alkalis (LD, DW, HC, ADW)	Neutralize or adjust acidity of other ingredients, make surfactants and builders more efficient	pH target for the final product	Ammonium hydroxide	0-10%
			Ethanolamine	0-10%
			Sodium carbonate	0-10%
			Sodium hydroxide	0-10%
			Sodium silicate	3-15%
Antimicrobial agents (LD, DW, HC)	Kill or inhibit growth of microorganisms that cause diseases or odor	Efficacy on targeted microorganisms	Pine oil	0-5%
		Potential for human skin sensitization	Quaternary ammonium cpds	0-5%
		Effect on surfaces to be cleaned	Sodium hypochlorite	0-1%
			Hydrogen peroxide	-
Antiredeposition agents (LD, DW)	Prevent soil from resettling after removal during washing	Efficacy of soil suspension or dispersion on fabric surface	Carboxymethyl cellulose	< 1%
			Polycarbonates	< 1%
		Interaction with surfactant system	Polyethylene glycol	< 1%
		Dissolution rate	Sodium silicate	3-15%
Binder (LD, ADW)	Increase cohesiveness of powder and hold them together to form granules	Hamaker constant	Polyethylene glycol	3-6%
		Young's modulus	Polyvinylpyrrolidone	3-6%
		Surface fracture energy	Polyacrylates	3-6%
			Acrylate copolymers	3-6%
Bleaches (LD, DW, ADW, HC)	Remove stains, chlorine bleaches also disinfect	Bleaching power	Sodium hypochlorite	0-1%
		Biocidal efficacy	Sodium perborate	0-13%
		Potential of color fading or fabric damage	Sodium percarbonate	-
		Ease of incorporation into formula		

LD = laundry detergents, DW = dishwashing liquids, ADW = automatic dishwasher detergents, HC = household cleaners, FC = fabric conditioners

Table 7. Typical additives used in detergents (continued).

<i>Additive</i>	<i>Desired function</i>	<i>Selection criteria</i>	<i>Examples</i>	<i>Typical amount</i>
Builders (LD, ADW, HC)	Enhance cleaning efficiency of surfactant by reducing water hardness	Calcium binding capacity	Zeolite	20-30%
		Soil dispersibility	Citrate	0-4%
		Alkalinity	Polycarboxylate	0-5%
		Bleach stabilization and anticorrosion capability	Carbonate	5-30%
Colorants (LD, DW, ADW, HC)	Provide special identity to product, provide bluing action	pH and thermal stability	Pigments/dyes	< 0.1%
		Lightfastness		
		Risk of staining cleaned objects		
Corrosion inhibitors (LD, DW, ADW)	Protect metallic machine parts, china patterns, and metal utensils	Ability to inhibit corrosion	Sodium silicate	3-15%
Disintegrant (LD, ADW)	Facilitate the break-up of tablet	Dissolution rate	Sodium bicarbonate-citric acid	5-15%
Dye transfer inhibitors (LD)	Prevent dye transfer and preserve color of garments during washing	Complexing power	Polyvinylpyrrolidone polymers	0.05-0.5%
Enzymes (LD, DW, ADW, HC)	Break down and remove soil, also clarifies colors by removing fuzz	Efficacy	Amylase	0.2-1.0%
		Need for stabilization	Lipase	0.2-0.6%
			Protease	0.1-1.5%
			Cellulase	1-3%
Fabric softeners (FC)	Impart softness and reduce static electricity in fabrics	Ability to reduce static electricity	Quaternary ammonium compounds	10-15%
Fluorescent whitening agents (LD)	Create a brightening effect	Substantivity on fabrics	Bistriazinyl derivatives of 4,4'-diamino-stilbene-2,2'-disulfonic acid	0.1-0.5%
Hydrotropes (LD, DW, HC)	Maintain product homogeneity	Compatibility with other ingredients like bleaches	Cumene sulfonate	0-10%
		Ability to increase surfactant solubility	Ethyl alcohol	-
		Color and odor	Toluene sulfonates	0-10%
			Xylene sulfonates	0-10%
Opacifiers (LD, DW, ADW, HC)	Make product opaque, provides a special effect	Ability to block UV rays	Polymers	0-3%
			Titanium dioxide	0-3%

LD = laundry detergents, DW = dishwashing liquids, ADW = automatic dishwasher detergents, HC = household cleaners, FC = fabric conditioners

Table 7. Typical additives used in detergents (continued).

Additive	Desired function	Selection criteria	Examples	Typical amount
Perfumes (LD, DW, ADW, HC, FC)	Mask base malodors of ingredients and soils, provide pleasant odors to clothes or room	Ability to deliver a specific smell Target pH of the final product	Perfume blends	0-1%
Preservatives (LD, DW, ADW, HC, FC)	Guards against product aging by decay, discoloration, oxidation, and bacterial attack	Ability to decrease water availability	Butylated hydroxytoluene Ethylene diamine Glutaraldehyde	0.05-0.2% 0.05-0.2% -
Rheological modifiers (LD, DW, ADW, HC, FC)	Improve flow properties of product, enhance consumer appeal, assist manufacturing	Rheological behavior	Clays Polymers Sodium silicate Sodium sulfate Solvents	0.5-2% 0.5-2% 3-15% - 0-5%
Solvents (LD, DW, ADW, HC, FC)	Prevent separation or deterioration of ingredients in liquid products, dissolve soils, clean without leaving residues	Ability to dissolve ingredients Cost	Ethanol Isopropanol Propylene glycol	0-50% 0-50% 0-5%
Suds stabilizers (DW, HC)	Give more suds when suds level is an important indicator of cleaning power	Ability to lower the <i>CMC</i> of the surfactant system	Alkanolamides Alkylamine oxides	0-5% 0-5%
Suds suppressors (LD, DW, ADW, HC)	Limit suds amount when suds will interfere with cleaning	Sensitivity to wash temperature, water hardness, and builder system Efficiency on the surfactant system	Alkyl phosphates Silicones Soap	0-5% 0-5% -

LD = laundry detergents, DW = dishwashing liquids, ADW = automatic dishwasher detergents, HC = household cleaners, FC = fabric conditioners

main function, selection criteria, examples, and typical concentration. The selection of additives depends heavily on product form and the presence of other ingredients. For example, enzymes are more often applied in powered detergents and less used in liquid detergents where they are less stable. Since the performance of enzymes can be easily influenced by water hardness, chlorine content, temperature, pH, ionic strength, bleaches, surfactants, and

proteases present [13], neutral salts or organic solvents are often needed to protect the enzymes [14]. The presence of solid particles such as abrasives in a liquid product often calls for the addition of thickeners to stabilize the suspension.

Some additives are necessary because they give the product the desired psychological appeal. For example, rheological modifiers can be used to increase viscosity so as to deliver a rich and concentrated product image [15]. Colorants are added to deliver the consumer-preferred color, which varies with age, gender, culture, and so forth. The addition of appropriate perfumes also makes the product more appealing to consumers, as perfumes can affect human mood and emotion [16]. The use of suds stabilizer or suds suppressor for foam control is also important; for instance, dishwashing liquids should produce more foam as it is a sign of cleaning power to consumers, whereas laundry detergents need less foam or else problems of rinsing or damage to the machine can occur. In general, each additive chosen should be safe for human use, cost-effective, as biodegradable as possible, and compatible with each other. For instance, acid dyes forming insoluble complex with cationic surfactant is not desirable. The additives should not harm the stability of the surfactant system that has been carefully chosen with phase behavior considerations.

Table 8 lists some heuristics for selection of additives. Understanding the mechanism by which the additives perform the desirable functions is very helpful in the selection process. For example, abrasives provide scrubbing action through friction between solid particles and the surface to be cleaned. Therefore, a suitable material is selected based on hardness. Binders keep powders together in tablets by rendering sufficient strength against compaction stress. Thus, the selection is based on material properties such as the Hamaker constant, Young's modulus, and surface fracture energy, which dictate the relative magnitude of various forces that hold the particles together [6]. Chemical properties such as degree of substitution (DS), which indicates the number of substituents attached to a monomer unit, is also widely used as selection criteria. Rheological modifiers can be selected by targeting the desired rheological behavior, such as a sufficiently high viscosity to support a stable suspension or thixotropic behavior for easier application [4].

The increasing popularity of biodegradable materials, which are more susceptible to microbial attack, has boosted the demand for preservation. If the product does not already contain ingredients that are themselves preservatives, such as cationic surfactants, acids, or bases, preservatives may need to be added. The required level of preservatives can be related to water availability (AW), which is defined as the ratio between the water vapor pressure over a substance and the water vapor pressure over pure water at the same temperature [17]. In general, an AW of below 70% should be targeted to prohibit microorganism growth [18].

Table 8. Heuristics for additive selection.

Selection of abrasives
<ul style="list-style-type: none"> Choose abrasives that are hard enough to assist cleaning but not too hard to scratch the surface, preferably with a hardness of about 3 in the Mohs scale [10].
Selection of acids/alkalis
<ul style="list-style-type: none"> Choose acids or alkalis to render the optimum pH for best performance of surfactants and enzymes (typically 6-8 for dishwashing liquids, 9.5-11 for laundry detergents, and 8-12 for all-purpose household cleaners). Choose acidic formulations for products designed to dissolve soap scum, hard water spots, stains, rust, or encrustations that are mainly calcium or magnesium salts [10]. Choose alkaline formulations for products designed to remove oils and organic soils or to treat acid-sensitive surfaces such as marble.
Selection of antimicrobial agents
<ul style="list-style-type: none"> Choose hypochlorite, which is the most inexpensive and effective disinfectant, for application on clean surfaces, as disinfecting capability of hypochlorite decreases dramatically with presence of proteins and soils. Consider adding metasilicate to reduce the corrosive effect of hypochlorite, or use a less active agent such as hydrogen peroxide, for application on metallic surfaces. Consider using quaternary ammonium compounds if the product is intended to be used at pH = 8-9 and in the absence of anionics, proteins, and milk residues. Their germicidal activity increases in the order of monomer = dimer < trimer < tetramer < polymer, with a peak of efficacy for C₁₂ – C₁₆ compounds [17]. Do not use quaternary ammonium compounds in products designed to clean cement, synthetic rubber, and aluminum because of possible surface damage. Consider using anionic and amphoteric surfactants to enhance the performance of antimicrobial agents, since they make the cell wall of microorganisms more permeable to disinfectants. Consider using organic complexes like iodophors and povidone-iodine that get trapped in surfactant micelles and release iodine as a disinfectant upon dilution, for products that contact human skin.
Selection of antiredeposition agents
<ul style="list-style-type: none"> Consider using methylcelluloses with high degrees of substitution ($DS \sim 2.6$) and low molecular weights (~ 5000) for soil removal applications, since they were found to have good antiredeposition activity while minimizing the interference with soil removal [19]. Use carboxymethylcellulose only in small amount in unstructured liquid products, since it has low aqueous solubility. Do not use ester-based antiredeposition agents for applications under high temperature or alkaline conditions, since they will hydrolyze.
Selection of binder
<ul style="list-style-type: none"> Choose binder materials that melt at 40°C or above, which is above the ambient temperatures of most countries, but not above 80°C for processing convenience.

Table 8. Heuristics for additive selection (continued).

Selection of bleaches
<ul style="list-style-type: none"> • Choose peroxygen bleaches over hypochlorite to minimize color fading or fabric damage. • Choose oxygen bleach over chlorine bleach if the product contains enzymes or perfumes. • Choose peroxycarboxylic acids or peracids over peroxygen for applications at low or ambient temperatures and neutral pH. • Separate peroxygen bleaches, hydrogen peroxide, or its sources like sodium perborate or sodium percarbonate from water to prevent premature reaction, such as by suspending the solids between surfactant lamellae in the structured liquid. • Use transition metal sequestrants such as phosphonates or nitrilotriacetic acid in the formulation containing peroxygen bleaches, since transition metals can catalyze the decomposition of peroxide.
Selection of builders
<ul style="list-style-type: none"> • Choose a builder and its amount depending on the aqueous solubility of the builder in the product besides its chelating power. For instance, do not use insoluble zeolites in unstructured liquid detergents. • Consider using phosphates where they are still permitted, because they are efficient builders with unsurpassed cost effectiveness and cleaning ability. • Do not use precipitation builders for laundry detergents, since they can leave behind insoluble deposits on clothes, causing damage on fabric and washing machine parts. • Use builders with $pK_{Ca} \geq 5$ with minimum molecular weight for liquid automatic dishwasher detergents. In general, the order of preference is: substituted malonate > malonate > succinate > acetate > propionate [20].
Selection of colorants
<ul style="list-style-type: none"> • Consider using acid dyes and polymeric colorants only for use in detergents. • Choose a colorant with high aqueous solubility to give an attractive well-dispersed color to the product. • Choose a suitable colorant by also considering degradation by light and staining of fabrics or surfaces.
Selection of corrosion inhibitors
<ul style="list-style-type: none"> • Choose builders like sodium silicates as corrosion inhibitors, since they can form barrier on metal or porcelain enamel surface. • Avoid using builders like sodium nitrilotriacetate or sodium tripolyphosphate as they will corrode metals.
Selection of disintegrants
<ul style="list-style-type: none"> • Choose a disintegrant that has high water affinity and solubility, to facilitate tablet breakup.
Selection of dye transfer inhibitors
<ul style="list-style-type: none"> • Consider using polyvinyl pyrrolidone (PVP), which is widely used because of its biological compatibility, low toxicity, high complexing power, and its inert behavior toward salts, acids, and thermal degradation [21]. • Do not use PVP with anionic surfactants like linear alkylbenzene sulfonate, since it is susceptible to deactivation by those surfactants. • Do not use PVP on acid red dyes [21].

Table 8. Heuristics for additive selection (continued).

Selection of enzymes
<ul style="list-style-type: none"> Choose enzymes which have alkaline optimum pH, are most effective at low wash temperatures of 20-40°C and stable for temperatures up to 60 °C. Do not use enzymes in formulations containing cationic surfactants, anionic surfactants like alkylbenzene sulfonates, and bleaches like hypochlorite and percarboxylic acids, since they can degrade enzymes. Use just enough amount of enzyme in the product, since the cleaning performance of enzymatic stains increases with concentration but saturates at high enzyme concentration.
Selection of fabric softeners
<ul style="list-style-type: none"> Choose fabric softeners based on their softening power, which decreases in the order of DHTDMAC > imidazoline quaternary > amidoamine quaternary ≥ TEA ester quaternary. Choose esterquats over DHTDMAC for environmentally friendly products, since they biodegrade more rapidly and are less toxic to aquatic life. Consider incorporating additives like monoalkyl quats, ethoxylated alcohols, ethoxylated amines, or solvents for ultras (concentrated fabric softeners), since they usually solve dispersibility problem stemmed from high concentration.
Selection of fluorescent whitening agents (FWA)
<ul style="list-style-type: none"> Use distyrylbiphenyl type and triazolylstilbene type, but not derivatives of 4,4'-diamino-stilbenzene-2,2'-disulfonic acid, for products containing chlorine bleach, due to compatibility. Avoid using FWAs with anionic surfactants, since they will enhance deposition of FWA on fabrics [22]. Adjust the desired solubility, substantivity, and other performance factors of the fluorescent whitening molecules, mainly CC/DAS or DASC-bis-triazinyl derivatives of 4,4'-diaminostilbenzene-2,2'-disulfonic acid, by adding different substituent groups like alkoxy, hydroxyl, or amino groups.
Selection of hydrotropes
<ul style="list-style-type: none"> Choose colorless and odorless hydrotropes like sodium xylene sulfonate, sodium cumene sulfonate, or ethanol with products for which color and odor are undesirable. Consider using urea in formulations with alkaline pH and for which ammonia smell is not a problem, since it is a cheap and effective hydrotrope. Choose alkyl-naphthalene sulfonates and sulfosuccinate esters as hydrotropes in formulations where foaming needs to be controlled, as they enhance solubility of anionic surfactants without increasing foam amount [20].
Selection of opacifiers
<ul style="list-style-type: none"> Choose the type and amount of opacifier depending on how much sunlight protection other ingredients need and consumers' preference on color.

Table 8. Heuristics for additive selection (continued).

Selection of perfumes
<ul style="list-style-type: none"> Choose a perfume blend that is compatible with other ingredients like hypochlorite bleach, peroxygen salts, and enzymes, and does not have potential of increasing product viscosity or causing phase separation (especially for structured liquids). Choose specific perfumes to mask malodors by identifying their source, such as ethoxylated alcohol nonionic surfactants (fatty malodors) and PVP dye transfer inhibitors (mouse-like odor). Consider using antimicrobial essential oils or perfumes extracted from plants in place of proprietary preservatives to make products with natural protection claims.
Selection of preservatives
<ul style="list-style-type: none"> Consider using preservatives in detergent products containing biodegradable raw materials with a neutral pH, especially low concentration liquid detergents. Use preservatives for products containing anionic surfactants as they are good nutrients for bacteria, but not for those containing cationic surfactants with nonionics as they can act as preservatives. Do not use formaldehyde and formaldehyde donors as preservatives, as their safety is doubtful. Do not use brominated nitropropanes/dioxanes for applications at pH above 8 or temperature above 60°C because of decomposition, or with secondary or tertiary amines or amides because of formation of health hazards [17]. Consider using dimethylhydantoin to have protection against bacteria, and iodopropylbutyl-carbamate (IPBC) against molds and yeast. Use their mixture for lower usage and cost-effectiveness.
Selection of rheological modifiers
<ul style="list-style-type: none"> Choose nonionic polymers for products containing electrolytes, but not for those containing acid, base, peroxide, persulfate, or hypochlorite as they may be unstable with these substances [15]. Use anionic polymers such as polyacrylic acids cross-linked with allyl ethers of pentaerythritol or sucrose as thickeners, if a gel structure and pseudoplastic (shear-thinning) properties are desirable. Consider adding colloidal alumina to further increase the viscosity at pH ~13 [15]. Do not use cationic polymers for products containing anionic surfactants, strong oxidizing agents, or electrolytes. Consider using organic thickeners such as carboxymethyl cellulose and hydroxyethyl cellulose with different substitution level per ring to obtain the desired thixotropy and water solubility behavior.
Selection of solvents
<ul style="list-style-type: none"> Choose a solvent that can dissolve all active ingredients and soften grease to facilitate its removal. Choose solvents with high volatility for spray products such as glass cleaners, so that product application would leave no streaks or residues. Consider using naturally extracted solvents like pine oil and d-limonene for environmentally friendly products. Use glycol ether to enhance shine on vinyl surface.

Table 8. Heuristics for additive selection (continued).

Selection of suds stabilizers
<ul style="list-style-type: none"> • Choose nonionics as suds stabilizers for use with foaming surfactants that are ionic. Prefer those with higher ability to lower the critical micelle concentration (CMC) of the foaming surfactant. • Do not use electrolytic suds stabilizers for products with nonionic surfactants, since it has no effect. • Choose macromolecular compounds like water-soluble polymers and proteins over surfactants and electrolytes as foam stabilizers for products with enhanced skin feel and skin mildness.
Selection of suds suppressors
<ul style="list-style-type: none"> • Consider using long chain soaps for applications at temperatures $> 60^{\circ}\text{C}$, and shorter chains (C12-C14) for application at low temperatures. Use in a mixture with ethoxylated fatty alcohols to enhance efficiency. • Do not use soap as antifoam for products with nonionic surfactants, since it has only limited effect.

8.2.3 Step 3: Design of Manufacturing Process

The process of detergent manufacturing typically involves first production and then isolation of the active ingredients. The ingredients will then be mixed together to form the final product with the desired microstructure in processing steps which differ with different product form, as shown in Figure 3. Powder can be produced in bulk solid processing steps. Spray form, liquid form (which includes structured and non-structured liquid), and gel are all manufactured through dispersion processing. Tablet requires tableting and coating, and sachet involves the use of a particular machine that does the thermoforming, filling, and sealing.

The general flowsheet for a detergent manufacturing process is depicted in Figure 4. The process consists of five major steps: pre-treatment, mixing, structure formation, post-treatment, and packaging. The pre-treatment step is where ingredients get conditioned before mixing. Heating/cooling, drying/humidifying, washing, dissolution, surface modification, or particle size change may happen in this step [5]. Mixing is the most difficult unit operation in liquid detergent manufacture [23]. It involves bringing together various ingredients with different properties to form a mixture. The order of ingredient addition should be able to limit undesirable rheological properties and to promote the formation of the desired microstructure, which is the following step. Order of addition is particularly important for mixing hydrating species, which can have problems in the presence of specific salts [23]. Processing-sensitive ingredients, for instance some heat-sensitive additives like bleach, bleach activator, enzymes, fragrances, and high value surfactants, can be added during post-treatment. Finally, the final product is packaged for sale.

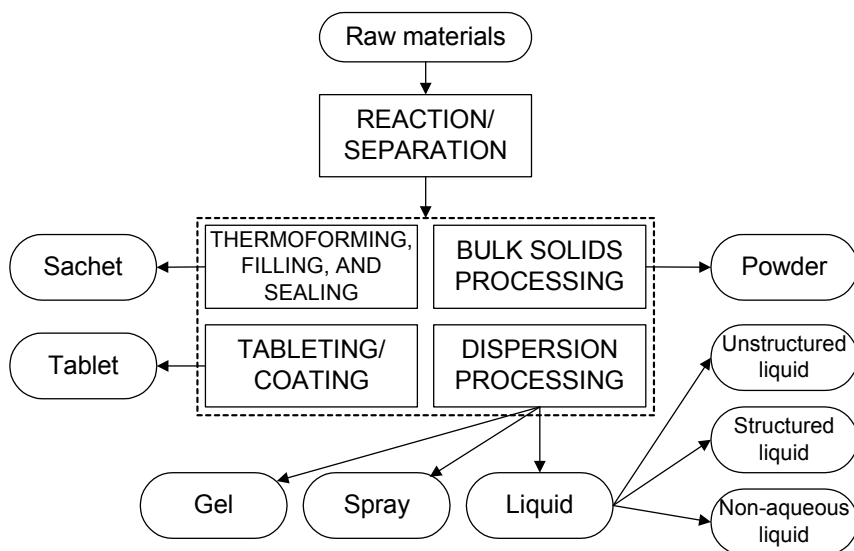


Figure 3. Unit operations in detergent manufacturing.

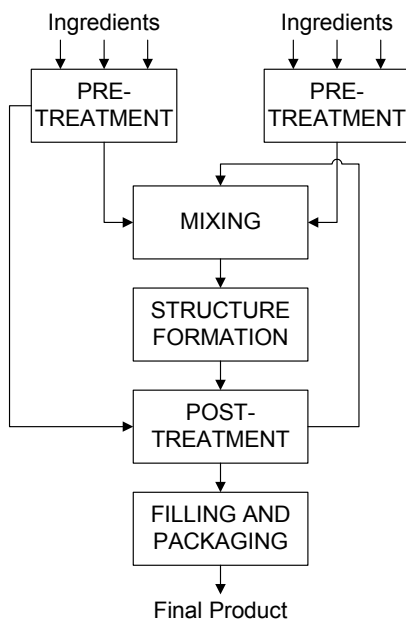


Figure 4. General flowsheet for a detergent manufacturing process.

Equipment units are then selected based on the unit operations for each of the five major processing steps in the general flowsheet. Table 9 shows the equipment units that can be used for various production methods for different product forms of detergents. Basically, while for tablet and sachet choices of equipment are only limited to tableting machine and TFS machine respectively, other product forms will have a variety of options depending on the nature of input substances. Table 10 lists the heuristics to aid the decision making when choosing one equipment unit against the other to perform a particular operation.

Table 9. Examples of equipment for manufacturing different product forms of detergents.

<i>Product Form / Feed</i>	<i>Unit operations</i>	<i>Examples of equipment</i>
<i>Powder</i>		
Aqueous solutions	Spray drying	Spray drying tower
Powder and flakes	Dry blending	V-shaped mixer, ribbon blender
Liquid and solids	Size enlargement	High shear mixer granulator, fluidized granulator (bubbling bed, spouted bed)
<i>Spray, Liquid and Gel</i>		
Soluble liquids	Mixing	Agitated vessel, in-line mixer
Liquid and insoluble solids	Dispersion	Agitated vessel, planetary mixer, Mixer-kneader
Immiscible liquids	Emulsification	Turboemulsifier (agitated vessel)
<i>Tablet</i>		
Powder	Tableting	Tableting machine
<i>Sachet</i>		
Liquid	Thermoforming, filling, and sealing (TFS)	TFS machine
<i>Powder and Tablet</i>		
Powder	Mixing	High shear mixer granulator, fluidized granulator (bubbling bed, spouted bed)
Powder or flakes	Size reduction	Jaw crusher, roller crusher, fluid jet mill
Powder	Screening	Vibrating screen
Liquid and solids	Coating	Spray drier, fluidized bed coater
<i>Spray, Liquid, Gel, and Sachet</i>		
Liquid and/or solids	Droplet/solid size distribution control	Colloid mill, tandem shear pipeline mixer

Table 10. Heuristics for equipment selection for detergents manufacture.

Granulator
<ul style="list-style-type: none"> • Use fluidized granulator to obtain granules of higher relative density (0.6 – 0.8), and high shear mixer granulator lower relative density (0.3 – 0.5) and thus faster solubility or easier dispersion. • Use fluidized granulator for high temperature feed. • Prefer high shear mixer granulator over fluidized granulator for handling cohesive materials or for higher throughput (up to 50 tonnes/hr compared to <500 kg for batch type fluidized granulator). • Prefer fluidized granulator over high shear mixer granulator if better temperature control for processing heat-sensitive materials is desired.
Solid blender
<ul style="list-style-type: none"> • Use continuous V-shaped mixer only for handling powder of diameter >0.01mm. For smaller powders, use ribbon blender. • Use V-shaped mixer for abrasive powders.
Liquid mixer
<ul style="list-style-type: none"> • Use static mixer or agitated vessel to mix separate phases to form a pre-emulsion. • Use planetary mixer for mixing suspensions with high solid volume fraction. • Use an agitated vessel equipped with a scraper for processing emulsions that are sensitive to heating or cooling, to minimized stagnant zones in the mixer.
Crusher
<ul style="list-style-type: none"> • Use fluid jet mill for producing particles of micron size range, roller crusher for mm to cm size range, and jaw crusher for cm size range.

The remaining task in the design of manufacturing process is to determine the operating conditions for each equipment unit just chosen. The design equations and typical operating conditions for selected equipment units are indicated in Table 11. Furthermore, for structured products, a set of *OV*s need to be selected so as to give a product with the desired *SA* as defined in the previous steps. In principle, each desired structural attribute (*SA*) in the product can be quantitatively related to the operating variable (*OV*),

$$SA_i = SA_i(OV_1, \dots, OV_p) \quad i = 1, 2, \dots, m \quad (3)$$

Such relationship can be obtained using the approaches of rigorous modeling, order-of-magnitude analysis, or black box analysis as suggested by Wibowo and Ng [5]. Examples of how *SA* relates to *OV* are given in Table 12. Note that due to the complex phenomena involved in these unit operations, shortcut empirical models that have some physical basis are often the most practical to describe the relationship. Unfortunately, such models are rarely available, making it difficult to quantify the relationship. For this reason, this part of the procedure is not emphasized in this article.

Table 11. Design equations and operating conditions for selected equipment units.

Equipment	Design equations and operating conditions	Ref.
Spray drying tower	Required drying air rate	[24]
	$L = \frac{1}{0.245(T_i - T_o)} [Ev(\lambda + 0.46T_o - T_f) + PC_p(T_p - T_f) + Q_L + (L_{aux} \times 0.24 \times (T_o - T_{amb}))]$	
	Residence time:	
	<ul style="list-style-type: none"> • 10 – 20 s for particles of few μm • 20 – 35 s for particles $\leq 180 \mu\text{m}$ • 35s or more for particles of 200 – 275 μm 	
	Typical diameter of droplets $\sim 100 \mu\text{m}$	[25]
Turboemulsifier	Typical pressure of atomizer $\sim 80 \text{ bar}$	[26]
	Hot air temperature: 250 – 400 $^{\circ}\text{C}$	
	Shear rate,	[27]
	$\dot{\gamma} = \frac{4\pi N}{1 - \left(\frac{D}{T}\right)^2}$	
	Mixing time, $\theta_m = f(N_n, N_{Fr}, S_i)$	[23]
Rotary tablet press	$N_{Re} = \frac{D^2 N \rho (8N)^{1-n}}{K} \left(\frac{4n}{3n+1} \right)^n \quad N_{Fr} = \frac{v^2}{gD}$	
	Impeller configurations:	
	<ul style="list-style-type: none"> • Open impellers or anchors for $\eta = 5,000\text{-}50,000 \text{ cP}$ • Helicals for $\eta = 50,000\text{-}500,000 \text{ cP}$ 	
	Typical number of stations per press = 20 – 40	[28]
	Typical throughput = 9,000 – 300,000 tablets/hr	
TFS machine	Tablet diameter = 10 – 30 mm	
	Typical maximum compression force $\sim 80 \text{ kN}$	
Fluid jet mill	Typical web width \sim up to 650 mm	[29]
	Typical throughput \sim up to 1,000 pieces/min	
Roll crusher	Minimum fluid velocity	[30]
	$u_{mf} = \sqrt{\frac{N_{Br}^* \sigma_t}{\rho_b \sin^2 \theta}}$	
Jaw crusher	Typical roll speed = 50 – 100 rpm	[31]
	Typical capacity $\sim 10 - 25 \text{ ton/hr}$ (6 mm particles)	
V-shaped mixer	Typical rotor speed $\sim 300 \text{ rpm}$	[32]
	Typical capacity = 1–30 ton/hr.	
Ribbon blender	Rotational speed, $N_C = 50 - 80\%$ of $N_{C,Cr}$	[33]
	$N_{C,Cr} = \frac{0.498}{\sqrt{R_{\max}}}$	
High shear mixer granulator	Powders filled to 30 – 50 % of vessel volume	
	Powders filled to $>70 \%$ of vessel volume	[33]
Fluidized bed granulator	Typical rotational speed $\sim 3,000 \text{ rpm}$	[34]
	Product granule size = 0.1 – 2 mm	
Fluidized bed granulator	$u_{mf} < u_o < 0.5u_f$	[35]
	Product granule size = 0.1 – 2 mm	[34]

Table 12. Examples of dependence of structural attributes on operating variables.

Structural attributes	Operating variables	Relationship
Powder (in spray drying tower)		
Mean particle size, D_{mean}	Air / liquid mass flow ratio, M_R Air density, ρ_a Liquid viscosity, μ_l Relative air liquid velocity at nozzle, v_{rel}	Kim-Marshall equation [26] $D_{mean} = 5356 \left[\frac{\sigma^{0.4} \mu^{0.32}}{(v_{rel}^2 \rho_a)^{0.57} A_G^{0.36} \rho_l^{0.16}} \right] + \left[\frac{\mu_l^2}{\rho_l \sigma} \right]^{0.17} \times \left[\frac{1}{v_{rel}^{0.54}} \right] \times \left[\frac{1}{M_R} \right]^m \times 3436$
Particle density, ρ_p	Atomizer wheel design	Wheels with curved vanes produce powders with higher density [24]
	Feed rate, f	Increases with increasing f
	Outlet air temperature, T_o	Decreases with increasing T_o
	Inlet air temperature, T_i	Decreases with increasing T_i
	Nature of feed	Suspensions give higher particle density than solutions
	Direction of air flow	Counter-current air flow gives higher particle density than co-current flow
Tablet (in rotary tablet press)		
Porosity, ε	Applied pressure, P	Empirical equation [36] $\ln \frac{1}{\varepsilon} = k_1 P + k_2$ <p>where k_1 and k_2 are constants affected by material properties and deformation</p>

8.3 Examples

Three examples are presented as below to illustrate the use of the systematic procedure outlined in this paper in developing and manufacturing detergent products.

8.3.1 Example 1: Automatic Dishwashing (ADW) Tablet with Gelatinous Inner-portion

Suppose a consumer product company wants to upgrade its automatic dishwashing tablet which is currently available in the market. The product form of tablet should be kept, but the new product should have faster dissolution in water. Moreover, the company experienced difficulty in attempting to include enzyme prills in the formulation as the prills could not sustain the high compaction pressure during tableting. The new product is expected to provide a solution to this problem. Other product qualities, which include minimum foaming during wash and no streaking on laundered dishes, should at least be as good as the current product.

Step 1: Since a clear product solution is desired, HLB_{Op} should be above 13 but still in the range of 3-15 to give some detergency (Figure 1). HLB_{Op} can be set at 14 since this time an HLB_{Op} near the high end is desirable for better surfactant dissolution in water to eliminate streaks or films on laundered dishes. The target cloud point is roughly set at 0°C in view of the fact that maximum detergency of nonionic is achieved when T_{cloud} is at $15\text{-}30^{\circ}\text{C}$ below the wash temperature, which is about 20°C in this case. A disintegration time of 1 hour (which is about 0.33g/min for the 20 g tablet) is set as a target. The equations in Table 3 can be used to estimate the appropriate tablet size and porosity from this targeted time.

Step 2: For faster dissolution in water, the inner-portion of the tablet is changed into the gel form. The gel product form is chosen as it guarantees faster dissolution than the solid form, and gel provides high enough viscosity to suspend some of the insoluble solid ingredients (Table 4). The gel form also makes inclusion of pressure-sensitive additives like enzyme prills possible. In addition, all the ingredients that used to interact with each other when placed in close proximity during tableting can now be put into the gel.

The original surfactant system and the additives are kept so that all the current product qualities will be maintained. However, by using the suggested performance indices, we can check if the current formulation really delivers the target product quality factors. The target HLB_{Op} is obtained with nonionic surfactant rather than ionics, which give too much foam for the current application (Table 5). With the target HLB_{Op} and T_{cloud} , the ideal surfactant is known to be alcohol ethoxylate derived from nonylphenol with 9 moles of EO per mole of alcohol.

Additives are then selected based on the desired functions (Table 7). To achieve high enough viscosity for gel formation, a rheological modifier is used instead of putting in more surfactant, as the cleaning duty is not supposed to be too heavy for an ADW tablet. Polyethylene glycol is chosen for its high commonness. Enzymes are needed for ADW formulations to break down food particles left on dishes. Thus protease and amylase prills are used and be included in the gel portion of the tablet. Effervescent disintegrants are also put into the inner-gel portion rather than the tablet outer-portion for better tablet disintegration. Table 13 provides a summary of the product formulation.

Step 3: The process flowsheet (Figure 5) for manufacturing the ADW tablet is synthesized based on the generic one in Figure 4. Since densities and sizes of the solid ingredients of the tablet body are very different, granulation is needed before tableting. For wet granulation (liquid ingredients will be added), either pan granulator or high shear mixing granulator can be used. The liquid ingredients can then be added to the solids in the granulator by spraying. The resultant granules will be compressed by a tablet press to form tablet. While the typical information in Table 11 provides an initial image of the suitable tableting machine, the equipment design should be discussed with vendors. Note that the tablet press should have different upper and lower punches to make the two halves of the tablet. The first half should contain an indentation as

Table 13. Summary of product formulation for Example 1.

Properties of Tablet Outer-portion		
Mass	20 g	
Dissolution time	0.33 g/min	
Constituent particle size	5 μm	
Formulation		
Builders:	Sodium tripolyphosphate	52.8 wt.%
	Carbonate	15.4 wt.%
	Silicate (also as corrosion inhibitor)	12.6 wt.%
Enzymes:	Protease	1.0 wt.%
	Amylase	0.75 wt.%
Bleach:	Anhydrous sodium perborate monohydrate	12.6 wt.%
Surfactant:	Primary alcohol ethoxylate	1.65 wt.%
	($T_{cloud} = 0^\circ\text{C}$, $HLB_{Op} = 14$)	
Perfume:	perfume blend	0.05 wt.%
Water		Balance
Properties of Gelatinous Inner-portion		
Mass	3.5 g	
Viscosity	75,000 cP at 25°C	
Formulation		
Rheological modifier:	Polyethylene glycol (MW = 8000)	4.0 wt.%
Organic solvent:	Glycerol triacetate	34.0 wt.%
Enzymes:	Protease prill	12.8 wt.%
	Amylase prill	7.2 wt.%
Disintegrant:	Anhydrous sodium bicarbonate	24.0 wt.%
	Citric acid	18.0 wt.%

a mold for holding the gelatinous mixture to be delivered, whereas the second half is not indented. The gel is prepared by mixing solid ingredients with melted polyethylene glycol (gelling agent) in an agitated vessel, which is chosen for mixing liquid with insoluble solids (Table 10). Gel form will be achieved after the mixture is cooled. The gel can be fed to the first half of the tablet body through a dosing valve with the dose for each tablet being monitored by a mass flowmeter. The two halves are then fused together by compression again in another tablet press. Finally the tablet will have post-treatment (coating) before being packaged as a product.

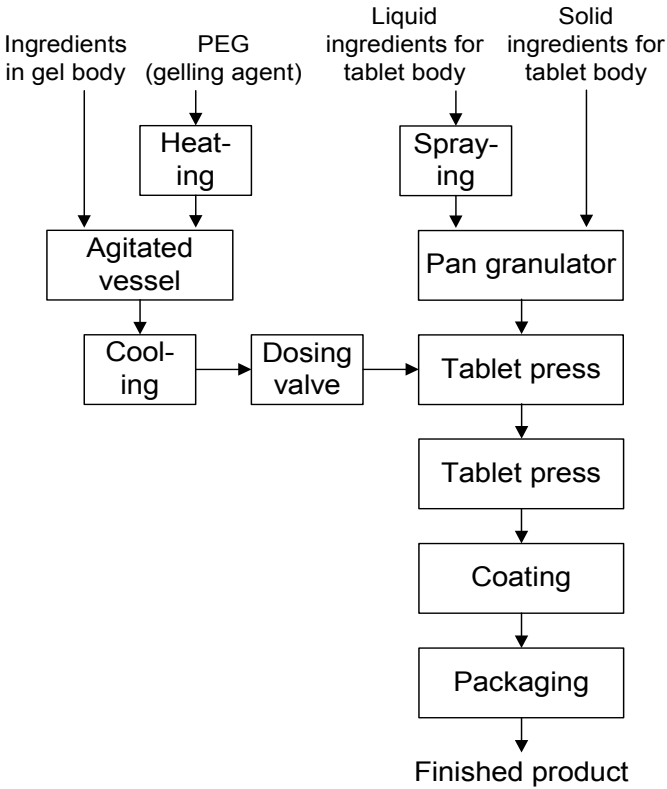


Figure 5. Flowsheet for manufacturing an ADW tablet with gelatinous inner-portion (Example 1).

8.3.2 Example 2: Sachet Household Cleaning Detergent

Ordinary all-purpose household cleaner is sold in concentrated liquid form, and requires dilution by consumers before application. This potentially causes either wastage or overdosing as the consumer is left alone to judge the correct amount of detergent to use. In addition, acid/alkali burns for consumers are not uncommon during the dilution process. Hence a demand for a more convenient product is apparent in the market.

Step 1: The dominant quality factors here are convenience and the ability to deliver the precise dosage for applications. Optimum HLB is an important factor for convenience (Table 2). As in example 1, an HLB value between 3 and 15 is desirable for the detergency property, preferably towards the high end to give clear appearance (Figure 1). Thus, HLB_{Op} is set to be 15.

Step 2: To deliver higher convenience to consumers, the product form can be changed to sachet, which allows delivery of the exact amount to be diluted in a specified amount of water. Finding suitable material for the sachet film is the most crucial in developing the product. The material should have sufficient dissolution upon contact with water for the release of detergent formulation, but it should be able to store the liquid formulation which does not necessarily have to be totally non-aqueous. It was found that polyvinyl alcohol served well as the sachet film material, as long as the formulation contains less than 10 wt% of water [37]. The film should be just thick enough to have sufficient mechanical strength against normal handling and for liquid storage, but thin enough to dissolve within the specified amount of time. The mass transfer-based Hixson-Crowell model (Table 3) can be used to estimate the maximum thickness from the desired dissolution rate.

The target HLB can be obtained by using a mixture of anionic surfactant ($HLB = 9.4$) and nonionic surfactant ($HLB = 16.7$) in the right proportions (1:3.75 based on the formula in Table 3). Such mixing of anionic and nonionic surfactants is expected to lower the individual CMC 's and thus an increase of the soil solubilization capacity. The surfactants in the product should be in spherical micelle phase to give a transparent/translucent appearance and small viscosity (Table 6).

Since the formulation is highly non-aqueous, the water-soluble inorganic builders are not suitable for use in this case (heuristic in Table 8). Dimethyl glyoxime is chosen for its organic nature and high enough efficacy as a chelating agent. To ensure that the requirement of water content <10 wt% is met, highly organic solvents are selected, including d-limonene which also serves as a source of the desired citrus smell. Alkanolamide is added as a suds stabilizer. Table 14 summarizes the formulation for this product.

Step 3: The process flowsheet for making the sachet is as simple as the one shown in Figure 6. The liquid content inside the sachet can be prepared by mixing all ingredients, which are all miscible this time, in an agitated vessel. The order of addition is important to ensure formation of the desired spherical micelle structure. First 2-butoxyethanol, hexylene glycol, d-limonene, and sodium lauryl sulfate are to be added, followed by dimethyl glyoxime and finally monoethanolamine, alkanolamide, and ethanol. The sachet form can be produced by the thermoforming, filling, and sealing (TFS) machine. The polyvinyl alcohol (PVA) film can be manufactured by feeding PVA resin into a film extruder. Additives like dyes, antioxidants, and UV stabilizers can be added to the extruder to enhance properties of the film. The PVA film is then processed into the TFS machine which first turns the film into pockets by vacuum, then fills up the pockets with detergent liquid, covers them with lids made with another PVA film, and finally seals by heat and compression. Finished products are obtained after routing out the pockets (sachets) and packaging.

Table 14. Summary of product formulation for Example 2.

Properties of External Film		
Material	Polyvinyl alcohol	
Thickness	5 mil	
Dissolution time	20 sec	
Properties of Internal Liquid		
Viscosity	40cP	
Phase	Spherical micelle	
Formulation		
Surfactant:	Sodium lauryl sulfate	4.0 wt.%
	(HLB = 9.4, T _{kraft} = 38°C)	
	Hexylene glycol	15.0 wt.%
	(HLB = 16.7, T _{cloud} = 95°C)	
Builder:	Dimethyl glyoxime	0.5 wt.%
Solvents:	2-butoxyethanol	13.5 wt.%
	Monoethanolamine	2.0 wt.%
	D-limonene (also as perfume)	15.0 wt.%
	Ethanol	47.5 wt.%
Suds stabilizer:	Alkanolamide	2.5 wt.%

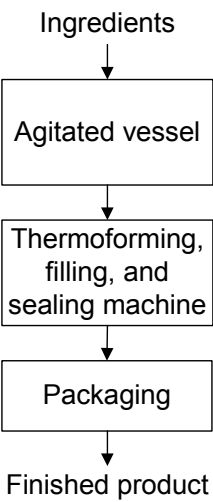


Figure 6. Flowsheet for manufacturing a household cleaning sachet (Example 2).

8.3.3 Example 3: Non-aqueous Structured Liquid Laundry Detergent with Suspended Surfactant Powder

A detergent company wants to make a liquid laundry detergent with high cleaning power. The new product is supposed to be a premium one with many qualities, hence it is expected to involve the use of many different ingredients. It is also desired to give consumers a creamy and rich impression.

Step 1: To enhance the “concentrated” image, the product can have a hazy appearance, which corresponds to HLB_{Op} of 10 – 13 (Figure 1). For a premium laundry detergent with a heavy cleaning duty, HLB_{Op} can be set at the low end of 10 for higher detergency. To achieve the desired high viscosity, sufficient amount of surfactants should be added so that they will be in the cylindrical micelle phase, which exhibits a viscosity of > 1000 cP with rheopectic behavior (Table 6). High viscosity of the liquid also allows suspension of insoluble solids, which in this case can contain more surfactant for higher cleaning power.

Step 2: The liquid detergent should be in structured form so that the compatibility of additives can be enhanced (Table 4). This will allow the application of more active ingredients in order to deliver more product qualities. The target HLB value can be achieved by mixing sodium linear alkylbenzene sulfonate ($HLB = 7.1$), which is mainly in the power form, and alcohol ethoxylate derived from C_{12} alcohol with 7 ethylene oxide units ($HLB = 12.5$) in proportions of 1:0.93. Ingredients are selected next based on the desired functions (Table 7), following heuristics in Table 8. Anhydrous citrate and carbonate are chosen as the builders as they possess a desiccating effect in addition to their chelating power. Sodium perborate is used as the bleach because of its high commonness. Its use necessitates the addition of DTPA, which binds with transition metal ions present in the wash water and prevents them from degrading the peroxygen bleach. NOBS is added as a bleach activator, so that sodium perborate will still function for wash temperatures below 60°C . To remove any food or starch that may be found on soiled garments, protease and amylase prills have to be added into the formulation. Rheological modifier is needed to further increase the viscosity for phase separation prevention. It was found that maleic-acrylic copolymer of MW 4,000-5,000 would suit this need [38]. Since too much foam will adversely affect the performance of the washing machine, suds suppressor should be added to the product. Alkyl phosphate is used for its high commonness. The formulation is summarized in Table 15.

Step 3: The process flowsheet is shown in Figure 7. The surfactant (NaLAS) powder can be made by spray drying of slurry containing NaLAS, sodium sulfate, sodium sulfosuccinate (hydrotrope), and water, after premixing them in an agitated vessel. A screen is then used to control the PSD of the powder. Any undersized or oversized solids are fed back to the mixing vessel with the rest being mixed with the non-aqueous structured liquid. This time based on the ingredients information, the order of addition of chemicals in producing the

Table 15. Summary of product formulation for Example 3.

Properties of the final product		
Viscosity	3000 cP, rheopectic	
Phase	Cylindrical micelle	
Formulation of final product		
Surfactants:	Sodium linear alkylbenzene sulfonate (NaLAS) powder ($HLB = 7.1$, $T_{krafft} = 31.5^{\circ}\text{C}$)	20.26 wt. %
	Alcohol ethoxylates (C_{12} alcohol, $\text{EO} = 7$) ($HLB = 12.5$, $T_{cloud} = 62^{\circ}\text{C}$)	18.82 wt. %
Solvent:	Butoxy-propoxy-propanol (BPP)	18.82 wt. %
Builder:	Sodium citrate dihydrate	4.32 wt. %
	Sodium carbonate (particle size: 10-40 μm)	11.58 wt. %
	Diethylene triamine pentaacetic acid (DTPA) (chelating agent to protect peroxygen bleach)	0.77 wt. %
Bleach:	Sodium perborate	2.86 wt. %
Bleach activator:	Citrate-coated nonanoyloxybenzene sulfonate (NOBS)	8.49 wt. %
Rheological modifier:	Maleic-acrylic copolymer	11.58 wt. %
	Titanium dioxide (enhances elasticity)	0.54 wt. %
Enzymes:	Protease prills (200-800 μm)	0.77 wt. %
	Amylase prills (200-800 μm)	0.39 wt. %
Suds suppressor:	Alkyl phosphate	0.03 wt. %
Perfume:	Perfume blend	0.46 wt. %
Whitening agent:	Disodium 4,4'-bis-(2-morpholino-4-anilino-s-triazin-6-ylamino) stilbene disulphonate	0.31 wt. %
Properties of NaLAS powder		
Formulation		
Surfactant:	Sodium linear alkylbenzene sulfonate	85 wt. %
Diluent:	Sodium sulfate	11 wt. %
Hydrotrope:	Sodium sulfosuccinate	2 wt. %
Water		Balance
Number of phases:	2 (insoluble and soluble in non-aqueous organic liquids)	
Amount of insoluble phase:		17 wt%
Particle size:	0.4 - 2 μm	

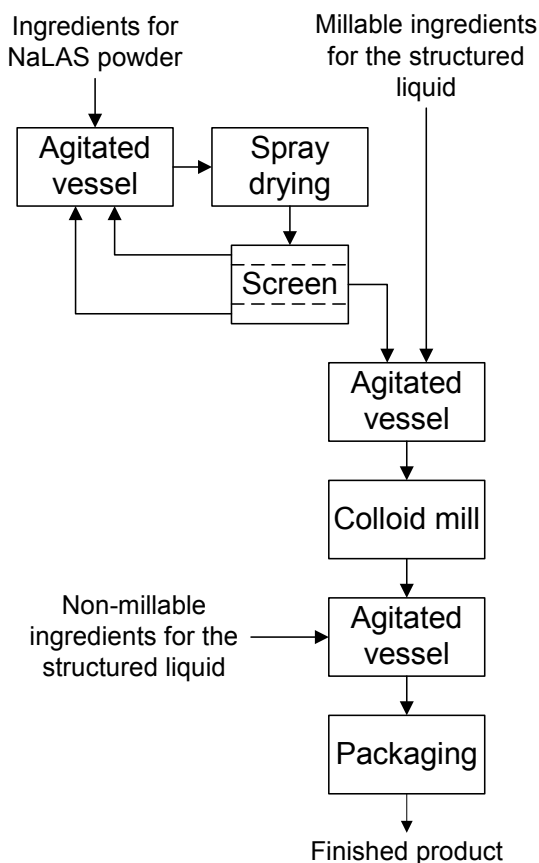


Figure 7. Flowsheet for manufacturing non-aqueous structured laundry detergent with surfactant powder (Example 3).

structured liquid is considered to be not important. However, since it is foreseen that milling will be required for the solid/liquid mixture to reduce the solid size for a higher yield stress of the product, only the millable solid ingredients such as carbonate, citrate, DTPA (builder), optical brightener material, and TiO_2 , together with the liquid ingredients constituting the structured liquid, should be added to the agitated vessel at this stage. The mixture is then passed through a fluid jet-type mill to reduce the particle size from 10-40 μm to the target 0.4-2 μm (Table 11). Colloid mill is selected for its high throughput and low capital and maintenance cost. The effluent will be mixed with the non-millable materials, such as the pressure-sensitive bleach activator and the enzyme prills, in an agitated vessel and be finally packaged as a product.

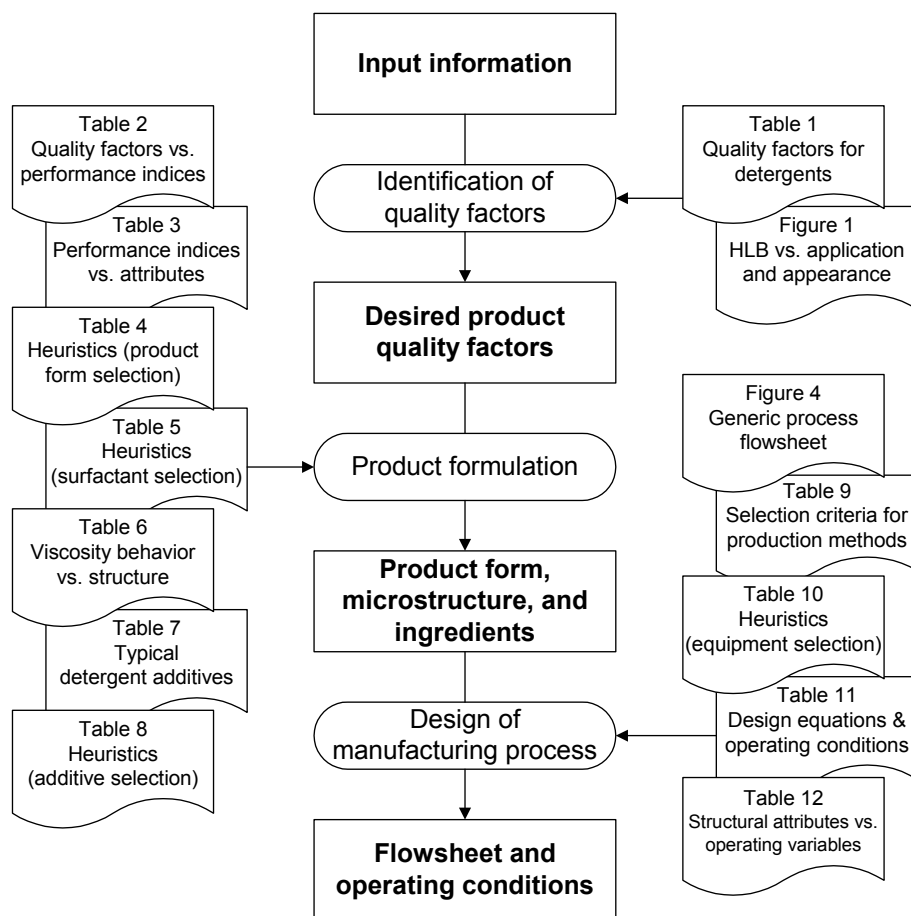


Figure 8. Systematic procedure for process synthesis and development of detergents.

8.4 Conclusions

The focus of the chemical engineering profession has gradually shifted from commodity chemicals to high-value-added products. For such specialty products, the ability for fast new product launches while at the same time maintaining superior product quality and performance that really differentiates one product from another is the key to success. Therefore, there is an urgent need for an efficient and effective product development for high-value-added chemical products. The product-centered process development procedure summarized in Figure 8 is an effort to meet this need for detergent products. In

contrast to the traditional emphasis on optimizing individual processes, this procedure adopted a new integrative product-centered approach which calls for close cooperation between the marketing personnel, the formulators who are very often chemists, and the chemical engineers in launching new detergent products that meet market needs in a timely manner.

References

1. K. Peyre, HAPPI, July 2004, <http://www.happi.com/current/July043.htm> (accessed November 2004).
2. M. McCoy, Chem. Eng. News, 80 (Jan. 21, 2002), 21.
3. S. J. Ainsworth, Chem. Eng. News, 72 (Jan 24, 1994), 35.
4. C. Wibowo and K. M. Ng, AIChE J., 47 (2001) 2746.
5. C. Wibowo and K. M. Ng, AIChE J., 48 (2002) 1212.
6. K. Y. Fung and K. M. Ng, AIChE J., 49 (2003), 1193.
7. T. Branna, HAPPI, June 2001, www.happi.com/special/jun013.htm (accessed August 2002).
8. M. J. Rosen, Surfactants and Interfacial Phenomena, 2nd ed., John Wiley & Sons, New York, 1989.
9. W. C. Griffin, J. Soc. Cosmetic Chemists, 1 (1947), 311.
10. K. Wisniewski, "Specialty liquid household surface cleaners," in K. Y. Lai, (ed.), Liquid detergents, Marcel Dekker, New York, 1997.
11. A. Sachdev and S. Krishnan, "Heavy-duty Liquid Detergents," in K. Y. Lai, (ed.), Liquid detergents, Marcel Dekker, New York, 1997.
12. A. Jacques, "Emulsions," in G. Broze, (ed.), Handbook of Detergents, Marcel Dekker, New York, 1999.
13. E. Gormsen, E. Marcussen, and T. Damhus, "Enzymes," in M. S. Showell, (ed.), Powdered Detergents, Marcel Dekker, New York, 1998.
14. A. Crutzen and M. Douglass, "Detergent Enzymes: A Challenge," in G. Broze, (ed.), Handbook of Detergents, Marcel Dekker, New York, 1999.
15. A. Farooq, "Rheological Modifiers for Aqueous Solutions," in G. Broze, (ed.), Handbook of Detergents, Marcel Dekker, New York, 1999.
16. J. S. Jellinek, Cosmet. Toilet., 109:10(1994) 83.
17. F. Siquet, "Disinfection and preservation in detergents," in G. Broze, (ed.), Handbook of Detergents, Marcel Dekker, New York, 1999.
18. R. Legenhausen, Course on Microbiological Quality of Water-based Product, Center for Professional Advancement, 1989.
19. E. Gosselink, "Soil release agents in powdered detergents," in M. S. Showell, (ed.), Powdered Detergents, Marcel Dekker, New York, 1998.
20. P. Gorlin and N. Dixit, "Liquid automatic dishwasher detergents," in K. Y. Lai, (ed.), Liquid detergents, Marcel Dekker, New York, 1997.
21. M. Grayson, et al. (eds.), Kirk-Othmer Concise Encyclopedia of Chemical Technology, Vol. 24, 3rd ed., John Wiley & Sons, New York, 1985.
22. O. Raney, in K. R. Lange, (ed.), Detergents and Cleaners: A Handbook, Carl Hanser Verlag, Munich, 1994.
23. R. S. Rounds, "Manufacture of Liquid Detergents," in K. Y. Lai, (ed.), Liquid detergents, Marcel Dekker, New York, 1997.

24. K. Masters, *Spray Drying Handbook*, 5th ed., Longman Scientific & Technical, Essex, 1991.
25. W. Adler and G. Thor, "Manufacture of Consumer Products," in J. Falbe, (ed.), *Surfactants in Consumer Products*, Springer-Verlag, Heidelberg, 1987.
26. K. Y. Kim and W. R. Marshall, *Amer. Inst. Chem. Eng. J.*, 17 (1971), 5757.
27. P. E. Miner, "Emulsion rheology: creams and lotions," in D. Laba, (ed.), *Rheological Properties of Cosmetics and Toiletries*, Marcel Dekker Inc., New York, 1993.
28. Casburt Ltd., <http://www.casburt.com/detergents.htm> (accessed August 2002).
29. Harro Höfliger Verpackungsmaschinen GmbH, <http://www.hoeffliger.com> (accessed August 2002).
30. C. Wibowo and K. M. Ng, *AIChE J.*, 47 (2001), 107.
31. Duo Ling-Watson, <http://www.dl-w.com> (accessed August 2002).
32. Arizona Construction Equipment Inc., <http://www.azce.com> (accessed August 2002).
33. K. Miyanami, "Mixing," in K. Iinoya, K. Gotoh, and K. Higashitani, (eds.), *Powder Technology Handbook*, Marcel Dekker, New York, 1991.
34. R. Martin, *Introduction to Particle Technology*, John Wiley & Sons, West Sussex, 1998.
35. I. Sekiguchi, "Granulation," in K. Iinoya, K. Gotoh, and K. Higashitani, (eds.), *Powder Technology Handbook*, Marcel Dekker, New York, 1991.
36. W. Pietsch, *Chem. Eng. Prog.*, 93:4 (1997), 24.
37. L. R. Dickler, and J. B. Ruck, U.S. Patent 6,136,776 (2000).
38. J. I. Kahn, M. A. Smerznak, W. A. M. Broeckx, I. J. M. J. Goderis, U. S. Patent 6,277,804 (2001).

Chapter 9

Design of the Dove® Beauty Bar

Michael I. Hill^a, Albert J. Post^b

^a*M. Hill & Associates LLC, Mahwah, NJ, USA*

^b*Unilever Research and Development, Trumbull, CT, USA*

9.1. INTRODUCTION

Dove® Beauty Bar was developed by Lever Brothers Co., a subsidiary of Unilever in the United States, in the 1950's. It has had an unusual product lifecycle in that it had a minor share of the U.S. soap market for over 25 years, after which it suddenly underwent a major expansion of market share, becoming the largest selling cleansing bar in the U.S. (as measured by dollar sales) [1,2].

While the Dove® formulation has undergone relatively minor changes since its launch in the U.S. in 1955, the marketing concept has seen major changes. Today's Dove® is marketed on a platform of extreme mildness to skin as evidenced by its neutral pH, and has been extended into different skin cleansing product forms (e.g. Dove® Body Wash) as well as other personal care products (e.g. Dove® Shampoo, Dove® Deodorant) [3]. However, the original problem definition had a very different focus.

The original product design problem was to formulate a non-soap cleansing bar that did not leave a bathtub ring. For those who are not familiar with this phenomenon, a bathtub ring is a deposit of insoluble calcium soaps ("soap scum") which result from the interaction of calcium salts in hard water with sodium soap from a common soap bar. Bathtub rings can even form in water that naturally contains little dissolved calcium salts ("soft water") as human perspiration can supply calcium salts. While the need to prevent bathtub rings may not seem significant today as most consumers prefer showers to baths, most consumers in the 1950's still took baths and typically scoured their

bathtubs to remove any residue of soap scum. Preventing the formation of a bathtub ring would therefore have saved significant labor.

By this time synthetic (non-soap) detergents had already been commercialized for laundry applications, and these proved superior to soap in that they worked well in hard water. This suggested that a cleansing bar containing synthetic detergents would similarly be insensitive to water hardness, and therefore not form a bathtub ring. Such non-scumming toilet soaps had already been introduced to the market, most notably Vel Beauty Bar (launched by the Colgate Palmolive Company in 1948) and Zest Beauty Bar (introduced by the Procter & Gamble Company in 1952) [4].

The main detergent in the Vel bar was sodium coco monoglyceride sulfate, whereas the Zest bar predominantly contained ordinary tallow/coconut soap, with a minor component of sodium glyceryl ether sulfonate [5]. However, the properties of these bars were considered deficient to ordinary toilet soap bars, either being significantly harsher to skin than ordinary soap, deficient in lather, or else having a draggy feel when wet. Hence, a need existed for a non-scumming cleansing bar with general use properties at least comparable to ordinary soap bars.

Dove® was launched in 1955 reaching a US market share of almost 3% by tonnage sold [1]. This chapter will review the set of product and process attributes that were identified as critical to a successful launch for Dove®, the laboratory techniques that were used to assess these properties, and the experimental program that identified the actual composition [6].

9.2. PRODUCT DESIGN PROBLEM

As noted above, the original product design problem was to formulate a cleansing bar that did not leave a bathtub ring. In addition to this primary attribute, however, the product had to be generally recognizable as a high qual-

Table 9.2-1. Secondary Properties (Relative to Ordinary Soap Bars)

PROPERTY
Firmness
Rich, creamy lather
Absence of grit
Not harsh to skin
No unpleasant odors or colors
Slippery feel when wet
Low mush rate
No cracking during repeated wet/dry cycles

ity personal cleansing bar if it was to be a success in the consumer marketplace. This implies a set of secondary product properties, which can be broadly interpreted as the absence of gross negatives compared to ordinary soap bars. Among the important properties, listed in Table 9.2-1, was mildness.

In addition to these *product* attributes, there was one *processing* attribute that could not be decoupled from the product composition: the bar needed to be manufactured on a standard soap production line without the need for significant capital investment. This is because soap manufacture is quite capital intensive [7,8], and Unilever wished to make use of its considerable capital investment.

A standard soap making production line of the time, which would also be perfectly acceptable today, included steam-jacketed mixing equipment, a chill roll (chilled roll mill with fixed blade) to solidify and form flake, a single stage extruder to produce noodles, a mixer for blending fragrance with the solid noodles, a three-roll mill for micromixing, a dual stage vacuum extruder (known in the soap industry as a plodder) to form solid billets, and a soap stamping press to form the final bar.

While there was a growing number of non-soap detergents that either were already commercialized (as for use in laundry applications) or else had viable commercial potential, it was decided early on to limit the compositional search space to compositions using sodium acyl isethionates (SAI) as the primary surfactant. This decision was based on an early assessment of a prototype bar containing SAI which had been described in a 1952 French patent for which Unilever had acquired the rights [9]. This prototype bar, with composition as described in Table 9.2-2, was referred to as the Monsavon bar.

According to internal Unilever assessments, although the Monsavon prototype bar was non-scumming and milder than ordinary soap bars, it was deficient in lather, subject to rancidity and poor color, and developed severe cracks after normal cycles of wetting and drying in a soap dish. These problems would all need to be resolved for the bar to be acceptable to consumers.

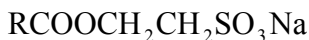
Table 9.2-2. Composition of Monsavon, anhydrous basis*.

Component	Role	Level
Sodium Acyl Isethionate (SAI)	Detergent (lather, cleansing)	80%
Stearic Acid	Binder	18
Lactic Acid	pH Modification	2

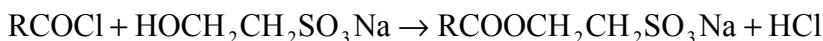
*Approximate bar moisture was 2%

The composition of choice would therefore contain SAI as the primary surfactant, a binder to ensure sufficient bar cohesiveness, and various other ingredients to modify bar properties as needed [6].

While a decision had been made to use SAI as the primary surfactant, the specific blend choice of SAI was subject to selection. SAI has the general chemical formula:



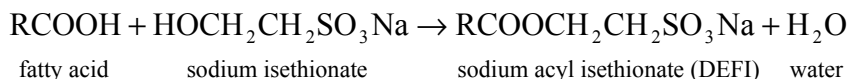
where R represents an alkyl chain. At the time these were made commercially by the anhydrous reaction of an acyl chloride (fatty acid chloride) with sodium isethionate [8]:



acyl chloride sodium isethionate sodium acyl isethionate hydrogen chloride

Hence, freedom to select the specific blend of SAI corresponded with the choice of acyl chloride (or, in turn, its source fatty acid) used in the manufacture of the SAI.

As a historical note, SAI for Dove was made by this acyl chloride process until a commercial process for direct esterification of fatty acid and sodium isethionate was developed by Lever Brothers Co. in the late 1950's. The SAI made by direct esterification is generally termed DEFI, an acronym for "directly esterified fatty isethionate". The DEFI reaction is follows:



The original DEFI process, including recommended catalysts and process conditions, was awarded US patent number 3.320,292 in 1967 [11]. By the mid-1960's, SAI for Dove was made exclusively by the DEFI process.

9.3. PROBLEM SOLUTION STRATEGY

In the 1950's there was a complete absence of models to describe the behavior of cleansing bars, and hence design problems were tackled by a completely experimental methodology.

Numerous compositions were explored, starting with the Monsavon bar. Once a composition was selected, a batch would be made at pilot scale (~15 kg) to produce prototype bars, and a set of attributes would be assessed. Based on the results, additional compositions would be proposed, some identified through scientific intuition, others through a comprehensive search of compositional possibilities.

Rather than assess all attributes for each prototype, a subset of properties was selected for use as a screening process. Protocols for screening tests that are broadly equivalent to those implemented by the Unilever product scientists during the development of Dove have appeared in the patent literature, and we note these references in Table 9.3-1. The tests were relatively easy to perform, and served to rapidly eliminate unsuitable compositions. Only if a prototype passed all screening tests would it be subject to the remaining property assessments, listed in Table 9.3-2.

Table 9.3-1. Screening Tests

PROPERTY	TEST DESCRIPTION, REFERENCE
Lather	Expert lather volume evaluation, U.S. Patent 6 846 787 [5]
Odor stability	U.S. Patent 6 255 265 [6]
Color	Ditto
Wet feel	Ditto
Mush	Ditto
Firmness	Penetration test, U.S. Patent 3 376 229 [7]
Processability	Extrusion rate, pilot scale, U.S. Patent 5 683 973 [8]

Thus prototype evaluation was performed using a variety of standardized tests, including various objective and subjective measures. Many of these laboratory tests were already being used to assess attributes of other products, either as quality control tests for ordinary soap bars or else in the development of detergent-based household products like laundry detergents or hard-surface cleansers.

Some tests, like lather volume, involved objective laboratory measurements. For example, a technician might produce lather by a prescribed washing procedure intended to consistently reproduce the same motions, and this lather volume would be measured in a graduated cylinder to give an objective measure [12]. Other tests, like wet bar feel, required the subjective measurement of trained assessors. For example, the wet feel of a bar would be subjectively characterized as draggy or slippery by an expert panel of evaluators [13].

Details for performing these evaluation tests can be found in the references cited in Tables 9.3-1 and 9.3-2.

Table 9.3-2. Additional Required Tests

PROPERTY	TEST DESCRIPTION REFERENCE
Mildness	Evaluation of erythema as a function of number of washes over several days. Testing has become more instrument dependent and quantitative. See Frosch for a review [16].
Grit or Sand	U.S. Patent 6 255 265 [13]
Cracking	Partial immersion in water for extended period followed by drying, and visual evaluation, see Colwell and Pflug (1991) [17].

9.4. PROBLEM SOLUTION

First and foremost among the deficiencies of the Monsavon formula was the poor bar lather. It had been observed that a 10% aqueous solution of the Monsavon bar had a pH of 3, whereas a 10% aqueous solution of ordinary soaps has a pH of 10. This acidity resulted from the presence of both lactic acid and residual hydrogen chloride, which was a by-product in the manufacture of SAI. Suspecting a connection with the poor lathering properties of the prototype, the pH of the prototype was raised from 3 to 7 by elimination of lactic acid and the addition of caustic solution, sodium carbonate, or sodium stearate [6,18].

While raising the pH gave some improvements in lather, more improvement was needed. Various co-surfactants, including alkyl sulfates, alkyl aryl sulfonates, and fatty acid taurides were effective in improving the speed of lather when present at levels of around 5%. Cost considerations led to choosing an alkyl aryl sulfonate, particularly sodium dodecyl benzene sulfonate, as it was already widely used in the formulation of laundry detergents.

Odor and color instability was traced to the choice of SAI. The original Monsavon composition used an SAI blend made from 80% coconut fatty acid and 20% tallow fatty acid. A characteristic alkyl chain length distribution for the resulting SAI is shown in Table 9.4-1.

Table 9.4-1. Chain Length Distributions[#] for Monsavon and SCI

Component	Level in Monsavon	Level in SCI
C8	7.7	7.8
C10	5.3	7.5
C12	39.0	51.6
C14	14.8	17.3
C16	11.9	9.2
C18	5.3	6.3
C18:1	12.2	0.9
C18:2	2.8	0.0
C18:3	0.3	0.0
C20	0.3	0.0

[#] Typical weight per cent chain length distributions based on 20:80 tallow:coconut fatty acid chain distribution specified for sodium acyl isethionate specified for the Monsavon bar [9], and the purely coconut fatty acid source for SCI.

This mixture, however, was subject to rancidity. Hydrogenating the fatty acids before making the SAI brought considerable improvement in odor and color stability, but at the expense of lather in cold water. Use of potassium acyl isethionates, while improving lather, resulted in unacceptably soft bars. It was finally determined that the best compromise lay in partially hydrogenating the coconut fatty acid (to 3-5 I.V.)¹ while simultaneously eliminating tallow fatty acid completely. Thus partially hydrogenated sodium cocoyl isethionate (SCI) was selected as the SAI of choice [6]. The alkyl chain length distribution for SCI is shown in Table 9.4-1.

Binders are included in synthetic detergent bars for cohesion and to plasticize the formulation during the manufacturing operations of milling, extrusion and stamping. The original Monsavon prototype was observed to crack excessively from repeated cycles of moisture adsorption and drying, and this was believed due to the use of stearic acid as the binder. Hence the experimental program examined the effect of using various commercial grades of fatty acids, soaps, and/or water soluble polymers as binders. A combination of long chain fatty acid and sodium soap allowed the formula to have the desired plasticity and low level of cracking, without losing processibility or mildness. The appropriate

¹ The degree of unsaturation of a fatty chain is classified by the iodine value (I.V.), defined as the weight of iodine that can react with 100 g of unsaturated material.

fatty acid level was established as 25-30% and the optimum level of sodium soap was established as 5-10%. For economic reasons, the long chain fatty acid that was selected was “triple-pressed stearic acid”, which is actually a eutectic mixture of 55% palmitic and 45% stearic acids. The sodium soap that was selected for use was ordinary toilet soap, made from a blend of 80% tallow and 20% coconut oil [6].

It was also observed that the pH of the finished bar was critical in controlling the amount of water absorbed by the bar and hence any subsequent cracking. It was found that when the pH was appreciably above 7, water absorption became excessive.

Water content is critical to the extrusion and stamping operations. Excessive water yields a very soft, sticky solid that is difficult to stamp and handle during packaging. On the other hand, low water content can yield a product with poor cohesivity. Too low a water content can also increase product viscosity during extrusion, raising the viscous dissipation of energy and thereby raising the product temperature to a point where the material becomes difficult to stamp. A target water level of 4-6% permitted the final extrusion to occur at a temperature of around 40 °C, yielding a material that could be handled by the soap stamping and packaging equipment [6].

Table 9.4-2. Original Commercialized Dove® Composition

Component	Level
Sodium cocoyl isethionate (SCI)	47-49
Stearic and coconut fatty acids	30-32
Sodium soap (80% tallow, 20% coconut)	6-8
Sodium isethionate	2-3
Alkyl benzene sulfonate	~ 2
Water	~ 4
Perfume, salts, miscellaneous	Balance

A penultimate prototype was tested by a large consumer panel of several hundred people to validate its comparative acceptability versus a competitor non-scumming soap bar and a typical tallow/coconut soap bar. All prototypes were unbranded and given to consumers in the same shape. The Dove® prototype performed better than the other products on most consumer perceivable measures. Minor modifications were made to the formula to correct some undesirable characteristics before introducing the product to market. The formula launched as Dove® in 1955 is shown in Table 9.4-2.

9.5 PROCESSING

While the Dove® composition described in Table 9.4-2 was processable at reasonable line speeds on a conventional soap processing line (roll mills, extruders, stampers), some equipment modifications were necessary. For example, whereas soap is normally mixed in large agitated tanks, the Dove® mixture had a much greater viscosity and therefore required use of a steam-jacketed kneader mixer such as those used to make bread dough, pastes or mastics.

Water level during processing provided an additional degree of freedom during design, as a higher level of water could be used as needed for viscosity modification during the early stages of processing, provided that any excess water could be removed in later stages of processing. It was found that if the batch was mixed in the temperature range of 95-115 °C, if the water level dropped too low a low viscosity dispersion formed which inhibited good mixing, but keeping the mixture at a water level of 4-8% allowed a high viscosity emulsion to form, which facilitated adequate mixing. The hot batch could then be cooled by dropping material on a chill roll or passing material through a water cooled mill. Solid chips or ribbons were refined, i.e. extruded into noodles, then blended with perfume in a ribbon blade mixer, milled and refined again, and finally extruded into continuous logs, cut and stamped into the desired shape.

Nevertheless, stickiness of the final composition made stamping difficult. This problem was mitigated by spraying a die lubricant of 6% aqueous sodium chloride on the chilled die faces.

9.6 DISCUSSION OF RESULTS

6.1 *Selection of Partially Hydrogenated Sodium Cocoyl Isethionate (SCI)*

The choice of alkyl chains used to prepare the SAI strongly impacts the bar lather, because the hydrophobicity of the surfactant is controlled by the molecular weight, degree of unsaturation, and branching of the chain. For example, it is known that an alkyl chain length of around C₁₂ has the right hydrophobicity to balance off the hydrophilicity of the isethionate head group. Longer alkyl chain lengths lead to less water solubility; shorter alkyl chain lengths lead to less surface activity [17]. Hence it is not surprising that the final choice of SCI is rich in C₁₂ chains, as shown in Table 9.4-1.

Odor and color stability problems were also related to the alkyl chains used for SAI. These could be traced to the oxidation of unsaturated carbons, such as oleic acid (C_{18} fatty acid with a single double bond between carbon 9 and 10, i.e. bond position 9 counted from the carboxyl carbon), linoleic acid (C_{18} fatty acid with two double bonds at position 9 and 12), and linolenic acid (C_{18} fatty acid with three double bonds at position 9, 12, and 15). Natural coconut fatty acid contains about 6% oleic acid, about 3% linoleic acid, and less than 1% linolenic acid. Tallow fatty acid contains nearly 44% oleic and about 6% of other unsaturates [20]. Partial hydrogenation of the coconut fatty acid used in the manufacture of SCI served to eliminate linoleic and linolenic acids for improved odor stability, while not eliminating oleic acid, which is important for good lather.

6.2 Binder Selection

Prototypes formulated with SCI, foam booster, stearic acid as a binder, and water produced acceptable lather, appropriate bar feel, and good plasticity for processing but showed cracking on repeated cycles of moisture adsorption and drying. Adjustment of the pH, which effectively sets the ratio of soaps to fatty acids in the binder, was found to be the key variable controlling cracking. Long chain fatty acids are water insoluble, though short chain fatty acids can melt in hot water. However, a higher pH converts more of the fatty acid to soap, and short chain soaps are quite water soluble. These soluble soaps lead to increased water penetration and finally to cracking upon drying of the bar. At pH 7, an insoluble molecular complex of sodium soap and fatty acid is favored [21], inhibiting water penetration and thereby preventing cracking.

6.3 Choice of Co-Surfactant

Various detergents were examined for their effect on lather properties. It was observed that alkyl aryl sulfonates (like sodium dodecyl benzene sulfonate) and alkyl sulfates (like sodium lauryl sulfate) had the biggest impact as foam boosters. This is not surprising, as both surfactants have head groups with high charge density, which is important for achieving rapid and stable foam [20].

9.7 CONCLUSIONS

In principle, the iterative experimental approach one would take today is no different than the one pursued by the product developers at Lever Brothers Co. in the early 1950's, though possibly accumulated data about surfactants, fatty acids, and soaps in the public domain might make ingredient selection some-

what easier today. Also, the scale of the batch size used for early prototype evolution in the present might be reduced because instruments for material property assessment (relevant to both use properties and processing) allow for smaller sample sizes to be tested. Perhaps 100 grams to a few kilograms of material might be required for characterization studies in early prototyping.

Nevertheless, the composition that was identified has stood the test of time. Minor modifications have been made to make improvements in clinically assessed mildness without sacrificing lather [22], but the Dove® composition remains largely unchanged to this day.

REFERENCES

1. J. Barnes, The Making (Or Possible Breaking) of a Megabrand, *New York Times*, 22 July 2001.
2. A.C. Neilson Corporate Report, Bar Soap Category, 9 July 2005.
3. <http://www.Dove.com>
4. L. Spitz, Soap and Detergent History, In: L. Spitz (ed.), *SODEOPEC, AOCS*, Champaign, IL, 2004, pp. 36-38.
5. M. Friedman, Chemistry, Formulation, and Performance of Syndet and Combo Bars, In: L. Spitz ed., *SODEOPEC, AOCS*, Champaign, IL, 2004, pp. 147-188.
6. R. C. Geitz, Detergent composition, US Patent No. 2 894 912 (1959).
7. E. Woollatt, *The Manufacture of Soaps, Other Detergents and Glycerin*, Ellis Horwood Ltd., West Sussex, 1985.
8. D. Baggini, F. Nizzero, L. Spitz, in L. Spitz (ed), *Soap Technology for the 1990's*, AOCS, Champaign, IL, 1991.
9. Societe Anonyme Chimex, Composition thermoplastique pour pain de toilette acide, FR Patent No. 1 059 341 (1952).
10. L. W. Burnette, Sulfoalkyl esters and amides of fatty acids, In: W. M. Linfield (ed.), *Anionic Surfactants*, part II, vol. 7, Marcel Dekkar, NY, 1976.
11. A. Cahn, H. Lemaire, R. Haass, Preparation of sulfonated fatty acid ester surface-active agents, US Patent 3 320 292 (1967).
12. T. J. Farrell, C. C. Nunn, Fatty acid soap/fatty acid bars which process and have good lather, US Patent 6 846 787 B1 (2005).
13. E. Van Gunst et al, Low synthetic soap bars comprising organic salts and polyethylene glycol, US Patent No. 6 255 265 B1 (2001).
14. R. Haass, V. Lamberti, Synthetic detergent bar, US Patent No. 3 376 229 (1968).
15. A. J. Post, F. S. Osmer, M. F. Petko, Mild bar compositions comprising blends of higher melting point polyalkylene glycols and lower melting point polyalkylene glycols as processing aids, US Patent No. 5 683 973 (1997).
16. P. J. Frosch, Irritancy of soaps and detergent bars, In: *Principles of Cosmetics for Dermatologists*, C. V. Mosby Co. (1982).
17. D. J. Colwell and J. J. Pflug, US Patent No. 5 017 302 (1991).

18. S. C. Farrington, Neutralization process, US Patent No. 2 967 189 (1961).
19. K. Holmberg, B. Jonsson, B. Kronberg, B. Lindman, Surfactants and polymers in aqueous solution, John Wiley and Sons, Ltd., Chichester, 2003.
20. G. L. Hasenhuettl, Fats and fatty oils, In: J. I. Kroschwitz and M. Howe-Grant (eds.), Kirk-Othmer Encyclopedia of Chemical Technology, vol. 10, J. Wiley and Sons, New York, 1993, pp. 267-8.
21. J. Lucassen, Hydrolysis and precipitates in carboxylate soap solutions, J. Phys. Chem., 70 (1966) 1824.
22. W. Narath, G. Ornoski, J. Corr, Enhanced processing of synthetic bar compositions comprising amphoteric based on minimal levels of fatty acid soap and minimum ratios of saturated to unsaturated soap, US Patent No. 6 121 216 (2000).

Chapter 10

Epitaxial Silicon Wafers using Plasma-Enhanced, Chemical-Vapor-Deposition

Talid Sinno and Warren D. Seider

Department of Chemical and Biomolecular Engineering, University of Pennsylvania, Philadelphia, PA 19104-6393, United States

10.1 ABSTRACT

This case study involves the manufacture of epitaxial silicon wafers, an *industrial chemical product* used in the production of *configured consumer products* such as integrated circuits. The *Stage-Gate Product Development Process* [1, 2] is applied for interaction with business decision-makers during the design stage. Emphasis is placed on process technology innovation; that is, a novel approach for the design of the plasma-enhanced, chemical-vapor-deposition (PECVD) reactor. For a 30-cm wafer, a new design strategy is suggested that minimizes the deposition time, for a given film thickness uniformity, by adjusting the geometry of the reactor. A moderately sized addition to an existing business is projected that takes polished wafers as a raw material and, using conventional processing techniques, along with a new reactor, produces epitaxial wafers. Profitability measures are computed as a function of wafer prices.

10.2 INTRODUCTION

When classifying chemical products, Seider et al. [3] identify three categories: (1) basic chemicals (commodity and specialty chemicals, bio-materials, and polymeric materials); (2) *industrial chemicals* (films, fibers, paper, ...); and (3) *configured consumer products* (dialysis devices, post-it notes, transparencies, drug delivery patches, ...). In the manufacture of epitaxial silicon wafers, a thin film of crystalline silicon is often deposited on a polished crystalline silicon

wafer to tailor the substrate for specific applications, such as microprocessor chips. This thin film, typically one of many deposited during the manufacture of an integrated circuit, is an *industrial chemical product* – one that is utilized in manufacturing configured consumer products.

10.3 STAGE-GATE PRODUCT DEVELOPMENT PROCESS

The *Stage-Gate Product Development Process* implements five steps involving design engineers, operating engineers, marketing and sales personnel, potential customers, and *business decision-makers (BDMs)*, as shown in Fig. 10.3-1. In the gate following each step, a *Real-Win-Worth (RWW)* evaluation is carried out. Positive results are presented to the *BDMs* who provide approval to proceed to the next step. In the *Real* evaluation, the extent of reality is assessed for a potential product. The *Win* evaluation assesses the competitiveness of the product with competitors in the market place (and the ability of customers' manufacturing facilities to accept the product, when applicable). Finally, the worth evaluation assesses the anticipated financial reward of the new product.

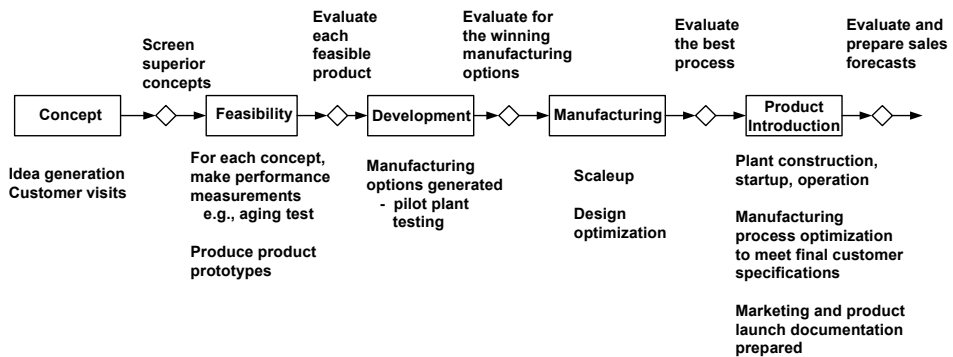


Figure 10.3-1. Stage-gate product development process

10.3.1 Step 1 – Concept Development

This first step, *Concept Development*, is one of the most creative, in which ideas are generated in an unconstrained atmosphere, keeping customer needs in mind. In this step, customer requests are translated into product requirements. Through an iterative process, the requirements are reviewed with the customers and refined as necessary. Product concepts are generated to achieve these

requirements. Then, for the best concepts, the *RWW* evaluation is applied. The *Real* analysis evaluates whether the perceived needs for the concept are technically realistic and whether the business opportunity is potentially realistic, given limited information at this stage. For the *Win* analysis, usually only patent information is available to address potential competition in the marketplace. For *Worth* analysis, only crude estimates of costs and profitability are possible at this stage. Inputs to the *BDMs* consist of the superior concepts, which they screen for acceptability.

For industrial products, such as films and fibers (woven and un-woven), the concept development stage is shown in Fig. 10.3-2. Under materials development, searches are carried out for chemicals and chemical mixtures having the desired properties and performance, and reaction paths for chemical synthesis. Under product/process technology development, often new methods are needed; for example, methods for creating multilayer films. And, finally, under manufacturing process development, an example of something new would be multilayer dies for producing multilayer polymer films.

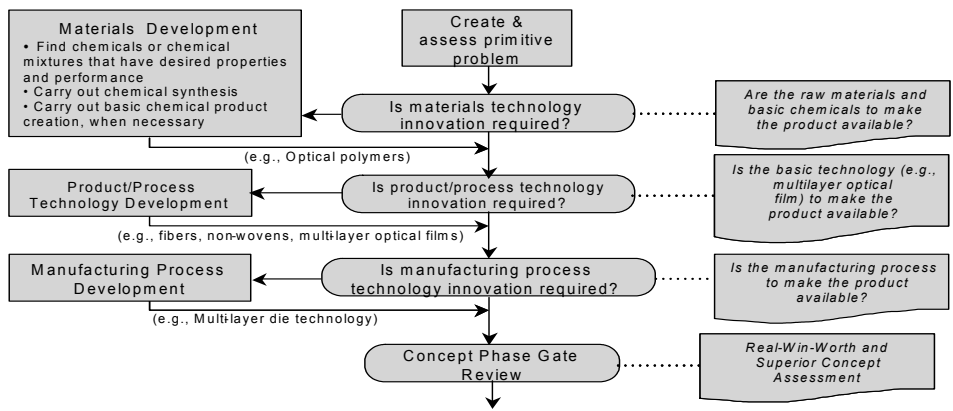


Figure 10.3-2. Concept development stage of industrial products.

Epitaxial thin films of silicon, to be deposited on crystalline silicon wafers, require no materials development. Other semi-conductor materials are possible, but silicon continues to be most cost-effective, principally due to the relatively

low cost of producing silicon wafers with the required quality. Moreover, the immense infrastructure already in place for silicon semiconductor technology dictates that this is likely to be the case for the foreseeable future.

In principle, the process design presented herein can be applied either to the deposition of amorphous Si films on any type of substrate for photovoltaic applications, or to the deposition of crystalline (epitaxial) films on polished silicon wafers typically grown by the Czochralski (CZ) technique. The latter process is used for eliminating any crystalline defects found in as-grown silicon wafers, as required for high value applications such as microprocessor chips. Examples of such defects are so-called crystal originated particles or COPs, which are microvoids formed by the condensation of supersaturated vacancies during CZ growth. These defects are strongly correlated with a decrease in gate-oxide integrity (GOI), which leads to reduced product yields.

The primary difference in the operating conditions for growth of crystalline as compared with amorphous material is the deposition temperature. In the current design, 500 K is assumed for amorphous film deposition, while higher temperatures in the range 700-950 K are required for epitaxial growth. The low-temperature amorphous film deposition first is used to optimize the process, while the high-temperature epitaxial deposition subsequently is used as the basis for a detailed economic analysis.

Innovations in process technology (second oval in Fig. 10.3-2) to deposit uniform layers of thin films are crucial to the success of epitaxial silicon films. During the Concept Development stage, the need for these innovations is identified, with the detailed design work done in the Manufacturing stage. Finally, the need for other manufacturing innovations are not identified in the Concept Development stage, because the process flowsheet for manufacturing silicon wafers, which involves plasma etching, robot loading and unloading of wafers, and vacuum pumps, is well known.

10.3.2 Steps 2-5 – Feasibility, Development, Manufacturing, and Product Introduction

For industrial products, the remaining four steps are elucidated in Fig. 10.4-1. After the *Concept Development* step (see Fig. 10.3-2), preliminary product design occurs in the Feasibility step of the Stage-Gate process – which is not applicable for epitaxial thin films of silicon, as prototype thin films are normally not needed.

In the *Development* stage, detailed product design is carried out. This is the key step for the chemical vapor deposition of thin silicon films. As described in the next section, to obtain uniform thin films rapidly, it is desirable to optimize the design of the plasma-enhanced, chemical-vapor-deposition (PECVD) reactor.

The *Manufacturing* stage involves the detailed design of the manufacturing process. This begins with the detailed design of the process units, including equipment sizing, cost estimation, and optimization. These are routine steps for the manufacture of epitaxial silicon films, and will be discussed in the *Manufacturing Process* section.

Finally, the *Product Introduction* stage is routine for this industrial product, and consequently, is not discussed herein.

10.4 OPTIMAL DESIGN OF PECVD REACTOR

During the *Development* stage, when designing the PECVD reactor, it is important to be aware of prior work on the design of CVD reactors. One study, carried out by Armaou and Christofides (1999), involves the design of a PECVD reactor to deposit *amorphous* thin films of silicon. In the present design study, this work is a basis for further design refinements and innovations. Both amorphous and crystalline film deposition processes are considered within the same overall framework and only the operating conditions are modified. The design strategy is first to use the conditions leading to amorphous growth to optimize the process, and then apply the resulting innovations to the epitaxial deposition case. In this way, it is possible to carry out a careful evaluation of the reactor modifications by comparison to existing results.

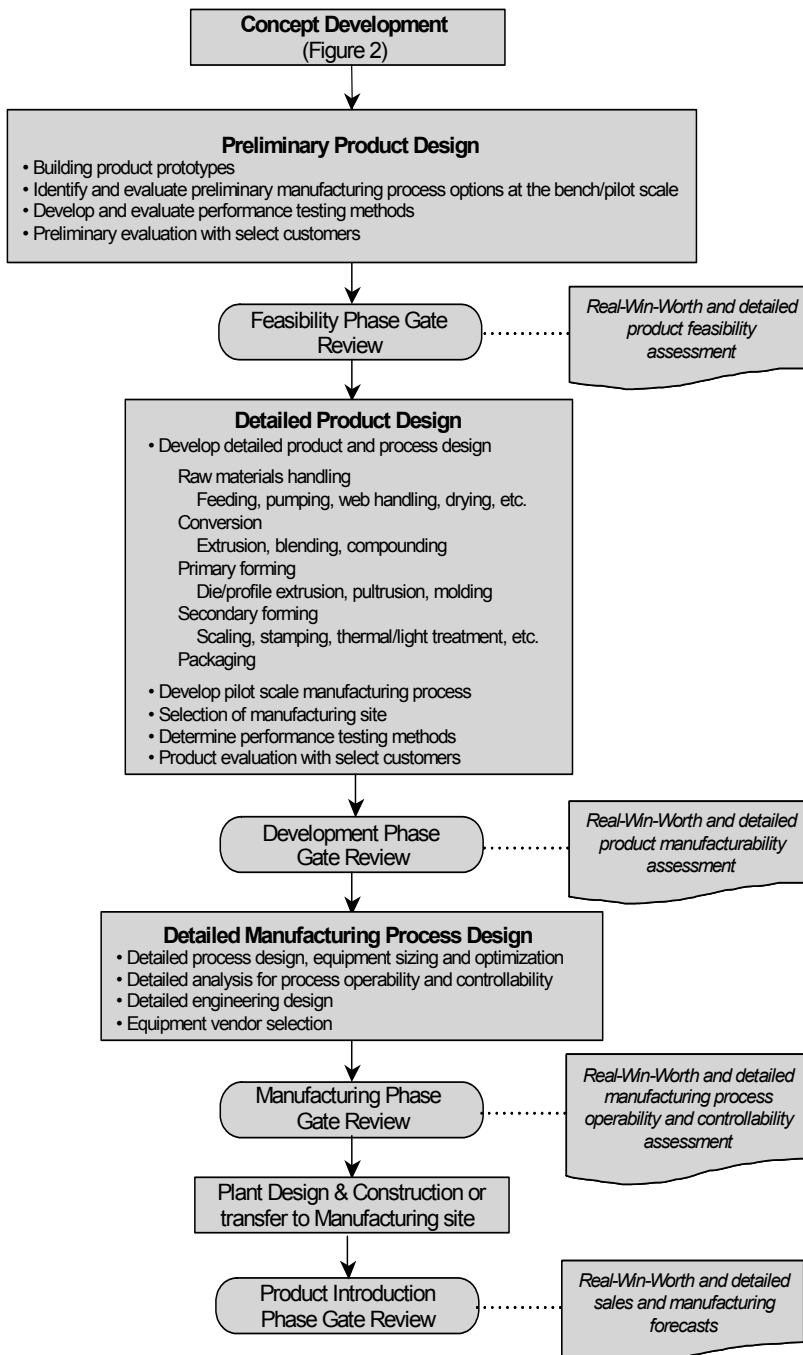


Figure 10.4-1. Steps in industrial product and process design

10.4.1 Amorphous Silicon Films

For the deposition of amorphous silicon films, lower temperatures require relatively low energy requirements. In one design, the base and walls of the CVD reactor are electrically heated to temperatures in the range of 600-700 K. Alternatively, electrodes create an electric field from a radio-frequency source, with electrons bombarding the gas molecules, creating a plasma, a chemically-reactive mixture of ions, electrons, and radicals. In these plasma-enhanced, chemical-vapor-deposition (PECVD) reactors, the chemical reactions occur at lower temperatures (500 K), with lower heating and cooling requirements and smaller stresses.

Armaou and Christofides (1999) present a two-electrode design for the deposition of 500-Å films on an 8-cm wafer, which sits on top of the lower electrode, as shown in Fig. 10.4-2. The reactor is fed with 10% SiH_4 (silane) in He at 1 torr through a showerhead. An RF power source, at 13.56 MHz frequency, is used to generate the plasma, which is transported by convection and diffusion to the surface of the wafer where reaction occurs to deposit amorphous silicon. Electrical heating elements are positioned below the wafer and along the walls to achieve a uniform temperature of the plasma and wafer at 500 K.

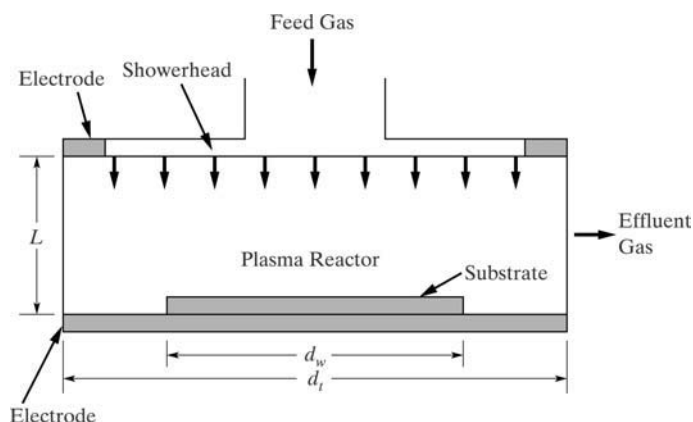


Figure 10.4-2. Cylindrical shower-head, electrode PECVD reactor

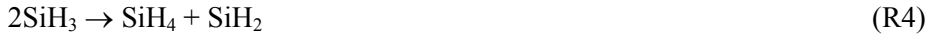
For design purposes, Armaou and Christofides use the following kinetic model. Initially, SiH_4 dissociates due to electron impact to form silylene (SiH_2), silyl radicals (SiH_3), and atomic hydrogen:



Then atomic hydrogen reacts with SiH_4 :



Silyl radicals diffuse toward the wafer surface where recombination reactions occur:



The intrinsic rates of consumption in $\text{mol}/(\text{cm}^3\text{min})$ of the four species are:

$$r_{\text{SiH}_4} = -k_1 n_e c_{\text{SiH}_4} - k_2 n_e c_{\text{SiH}_4} - k_3 c_{\text{SiH}_4} c_{\text{H}} + k_4 c_{\text{SiH}_3}^2 - k_5 c_{\text{SiH}_4} c_{\text{SiH}_2} \quad (1)$$

$$r_{\text{SiH}_2} = k_1 n_e c_{\text{SiH}_4} + k_4 c_{\text{SiH}_3}^2 - k_5 c_{\text{SiH}_4} c_{\text{SiH}_2} \quad (2)$$

$$r_{\text{SiH}_3} = k_2 n_e c_{\text{SiH}_4} + k_3 c_{\text{SiH}_4} c_{\text{H}} - k_4 c_{\text{SiH}_3}^2 \quad (3)$$

$$r_{\text{H}} = 2k_1 n_e c_{\text{SiH}_4} + k_2 n_e c_{\text{SiH}_4} - k_3 c_{\text{SiH}_4} c_{\text{H}} \quad (4)$$

where c is the concentration in mol/cm^3 and n_e is the electron density given by:

$$n_e \{r, z\} = n_e^{\max} J_0 \left\{ 2.405 \frac{r}{r_t} \right\} \sin \left\{ \frac{\pi z}{L} \right\} \quad (5)$$

Here, n_e^{\max} is the maximum electron density in the reactor, r is the radial position in the reactor, r_t is the radius of the reactor cylinder, z is the axial coordinate, L is the height of the reactor (distance between the two electrodes), and J_0 is the zero-order Bessel function of the first kind. Clearly, the electron density is a maximum at the center of the reactor ($r = 0$, $z = L/2$). The rate constants are:

<u>Rate Constant</u>	<u>Units</u>
$k_1 = 1.870 \times 10^{-11}$	$s^{-1}cm^3$
$k_2 = 1.590 \times 10^{-10}$	$s^{-1}cm^3$
$k_3 = 1.325 \times 10^{12}$	$s^{-1}mol^{-1}cm^3$
$k_4 = 9.033 \times 10^{13}$	$s^{-1}mol^{-1}cm^3$
$k_5 = 2.830 \times 10^{13}$	$s^{-1}mol^{-1}cm^3$

To simulate the PECVD process, a design team creates a PDE model involving momentum and mass balances, as summarized below. It is sufficient to assume the plasma to be a continuum, with physical properties of the gas constant (independent of position and time), negligible volume change of the reacting gases, and velocity and concentration fields symmetric about the reactor centerline (azimuthal symmetry).

Armaou and Christofides consider the design of a reactor having $L = 3.6$ cm, $r_t = 8.0$ cm, with a radius of holes in the showerhead, $r_h = 0.1$ cm, $N_h = 350$ holes in the showerhead, and a wafer having $r_w = 4$ cm. Silane is fed to the reactor at 50 cm³/min, uniformly distributed among the showerhead holes, and the maximum electron density is 2.0×10^{10} cm⁻³. At 1 torr and 500 K, the viscosity and density of the gas are 1.832×10^{-7} kg/(s-cm) and 1.030×10^{-9} kg/cm³. The silicon density is 8.292×10^{-10} mol/(Å-cm²).

The Navier-Stokes equations are solved first to determine the velocity field throughout the reactor, as described by Armaou and Christofides [4], and subsequently by Brass and Lee [5] using FEMLAB. Then, the species mass balances are solved to determine the concentrations of SiH₄ (1), SiH₂ (2), SiH₃ (3), and H (4), throughout the reactor. Finally, the deposition rate of silicon is:

$$r_{dep}\{t, r\} = \frac{1}{\rho_{Si}} \left[\sum_{i=1}^4 s_i D_i \frac{\partial c_i}{\partial z} \{t, r, 0\} \right] \quad (6)$$

where ρ_{Si} is the density of amorphous Si, and s_i is the fraction of the flux of species i toward the surface that leads to the deposition of amorphous silicon ($s_1 = s_4 = 0$, $s_2 = 1$, $s_3 = 0.4$), and the diffusion coefficients are $D_1 = 285.05$, $D_2 = 321.86$, $D_3 = 319.16$, and $D_4 = 2,107.75 \text{ cm}^2\text{s}^{-1}$.

For these conditions, Armaou and Christofides [4] determine the thickness profile, in Fig. 10.4-3, for the amorphous silicon film after 60 s, when the average thickness reaches 500 Å. When characterizing the non-uniformity of the film, the sharp increase in thickness calculated near the outer edge of the wafer is assumed to be due to the boundary conditions, which assume step changes to zero concentrations at the edge. Brass and Lee (2003) disregard the profile from $r = 3.6$ to 4 cm, and compute the non-uniformity as:

$$M_N = \frac{t_{\max} - t_{\min}}{t_{\min}} \times 100 \quad (7)$$

which gives $M_N = 19.2\%$, far in excess of the industrial target of 2-3%.

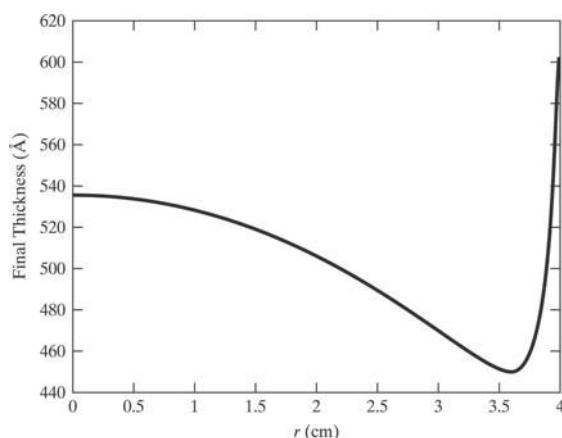


Figure 10.4-3. Thickness of amorphous silicon after 60 s.

To improve the uniformity, Armaou and Christofides [4] use individual PI controllers to adjust the flow rate of silane at several radial positions along the showerhead. Brass and Lee report that this gives a marked improvement in uniformity, with $M_N = 3.8\%$, but with a significant increase in the deposition time to 73 s.

To obtain better uniformity during smaller deposition times, Brass and Lee explore geometrical design changes in the reactor, recognizing that the rate of deposition can be increased as the radius increases by decreasing the time for SiH_2 and SiH_3 to reach the wafer. This can be accomplished by gradually reducing the reactor height as the radius increases, using the configuration shown schematically in Fig. 10.4-4.

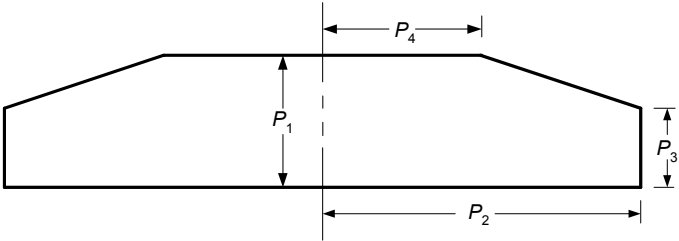


Figure 10.4-4. Schematic of PECVD reactor chamber for design optimization.

In principle, one can carry out a four-dimensional optimization in which the four parameters are varied subject to constraints ($P_3 \leq P_1$ and $P_4 \leq P_2$), to minimize the deposition time with the non-uniformity bounded; e.g., $M_N \leq 3$. However, objective function evaluations involve solutions of the Navier-Stokes and species balance equations and are computationally expensive. Instead, Brass and Lee carry out successive unidirectional optimizations, which show the key trends and lead to excellent designs. A summary of the observed trends is shown in Table 10.4-1. Both the deposition rate and the non-uniformity are monotonic functions of the geometric parameters within the bounds considered, with the exception that the non-uniformity goes through a minimum at optimal values of P_3 and P_4 .

Table 10.4-1. Summary of trends in the deposition rate and non-uniformity responses to increases in each of the geometric parameters in the reactor.

Parameter	Deposition Rate	Non-uniformity
P1 - ↑	↓	↓
P2 - ↑	↑	↓
P3 - ↑	↓	↓ then ↑
P4 - ↑	↓	↓ then ↑

Initially, Brass and Lee vary P_1 between 2.5 and 7 cm, observing a linear increase in τ (deposition time) to 105 s as P_1 increases, accompanied by a decrease in M_N to 16%. Then, they vary P_2 between 6 and 12 cm, observing decreases in τ and M_N , leveling in the vicinity of 60 s and 4-5%, indicating that large increases in P_2 are needed for small improvements. When they vary P_3 between 0.5 and 5 cm with $P_4 = 0$, $P_1 = 4$ cm, and $P_2 = 8$ cm, τ increases to 76 s and M_N is minimized near 3% at $P_3 = 1.5$ cm. Finally, they vary P_4 between 0 and 2.5 cm and obtain a minimum M_N at 1.5% and $\tau = 61$ s, values that are much improved compared with those obtained by Armaou and Christofides using PI control. The response of the non-uniformity to changes in P_4 is shown in detail in Fig. 10.4-5.

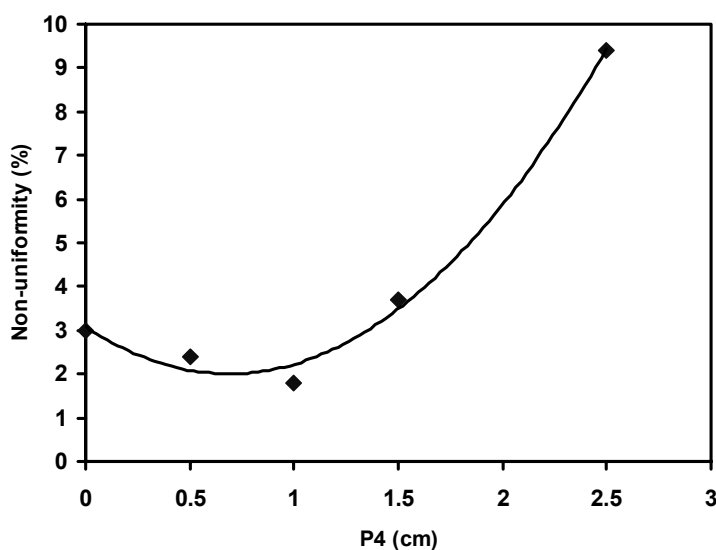


Figure 10.4-5. Dependence of non-uniformity on the P_4 parameter for a 8-cm diameter wafer.

Having completed these studies, Brass and Lee attempt a similar optimization to deposit 500-Å films on 30-cm wafers, which are increasingly being used in device fabrication. Note that the optimal design cannot be computed using a single scale factor because the convection and diffusion rates do not scale linearly with reactor size. For 30-cm wafers, diffusion resistances are greater and non-uniformity increases. When producing 30-cm wafers, Brass and Lee use $r_h = 0.1$ cm, $N_h = 4,922$ holes, and $r_w = 15$ cm, with silane fed to the reactor at 705 cm³/min. For these larger diameters, qualitatively similar results were

obtained, with the smallest M_N at 2.3% and $\tau = 86$ s ($P_1 = 6$ cm, $P_2 = 35$ cm, $P_3 = 5$ cm, and $P_4 = 5$ cm).

10.4.2 Epitaxial Silicon Films

Next, using this evolutionary approach, the design team tackles the deposition of epitaxial silicon on 30 cm wafers. Typically, 2,000-Å films are deposited on 700 μm wafers at higher temperatures to achieve crystalline films. As the temperature increases, both the deposition rates and the non-uniformity increase. Here, the diffusion resistance decreases less rapidly than convection resistance. For the design optimization, Brass and Lee increase the temperature to 923 K and adjust the properties and rate constants accordingly using literature estimates for the activation energies for each reaction. Note that, at these conditions, the deposition rate is increased from 6 Å/s for amorphous films to 34 Å/s for epitaxial films. For these films, the optimization begins at the optimal design for growth of 30-cm amorphous films. Brass and Lee observe the smallest M_N at 4.95% with $\tau = 62$ s ($P_1 = 6$ cm, $P_2 = 35$ cm, $P_3 = 3.75$ cm, and $P_4 = 0$ cm), as shown schematically in Fig. 10.4-6. Commercial epitaxial wafers are typically produced with about 4% non-uniformity. Hence, to achieve this in practice, it may be desirable to implement flow controllers. Note, however, that the demands on any flow controllers are greatly reduced relative to the base case because of the geometric optimization of the reactor.

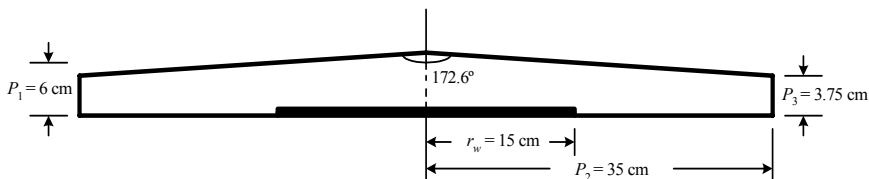


Figure 10.4-6. Schematic of PECVD reactor chamber geometry for deposition of epitaxial films on 30-cm diameter wafers. $P_4 = 0$.

10.5 MANUFACTURING PROCESS

Manufacturing processes are well developed for silicon wafers. To avoid particle contamination, compact clusters of processing units operate in 100-level clean rooms, which for small companies are often rented in larger complexes at approximately \$400/ft²-yr.

The principal components of a deposition cluster are shown in Fig. 10.5-1. To begin the manufacturing process, wafers are received in cassettes; that is, slotted holding cases containing 25 wafers. Note that larger diameter wafers (30 cm and larger) are often polished on both sides, providing greater “flatness”, which is crucial to maintain high uniformity levels. These are transferred from the holding cases into a cassette-loading unit by a machine (not shown). Once in this unit, the processing steps begin:

- Step 1. A vacuum is drawn at 1 torr over five minutes, using, for example, a Becker U 4.70 oil-based vacuum pump. Note that the vacuum pump resides outside of the clean room.
- Step 2. A dual-armed robot (e.g., an Endura VHP robot by Applied Materials) transfers one wafer to the plasma-etch reactor in 20 s. The robot is encased within a transport module that is evacuated to 1 torr. Based upon the Trikon Sigma fpx Deposition Cluster, it is estimated that 35.1 ft² of 100-level clean room area are required.
- Step 3. The plasma-etch reactor uses 705 SCCM/min of carbon tetrafluoride (CF₄), with electron bombardment, to remove oxidized species from the wafer surface in 3 s, at 500 K and 1 torr. The hot effluent gases are contacted with cooling water in a small 1-6 shell-and-tube heat exchanger containing 4 tube/pass. The cooled gases, at 310 K, pass through a vacuum pump into a water scrubber, integrated with a catalytic reactor (e.g., Trinity by Enviro-Matrix). The water scrubs the fluoride compounds and the reactor decomposes them. Only the plasma-etch reactor resides in the clean room, requiring 15.9 ft².
- Step 4. The robot transfers the wafer to a wafer-holding unit, in 20 s, which holds wafers at 1 torr, 288-303 K, and 25-75% relative humidity, until they are transferred to one of the two PECVD reactors. This unit requires 2.5 ft² of clean room area.
- Step 5. The robot transfers the wafer from the wafer-holding unit, in 20 s, to one of the PECVD reactors.

- Step 6. Helium and silane gases are transferred from small cylinders to one of the PECVD reactors, which deposits a 2,000 Å film, at 923 K and 1 torr, onto the wafer in 62 s, as discussed in the previous section. The hot effluent gases are contacted with cooling water in a small 1-6 shell-and-tube heat exchanger containing 4 tube/pass. The cooled gases, at 310 K, pass through a vacuum pump into an air combustion unit (e.g., Altair by Enviro-Matrix). Then, the incinerated gases are sent to the water scrubber, integrated with its catalytic reactor. They are scrubbed, together with the fluoride compounds, by water and further decomposed in the catalytic reactor. Only the PECVD reactors reside in the clean room, each requiring 15.9 ft².

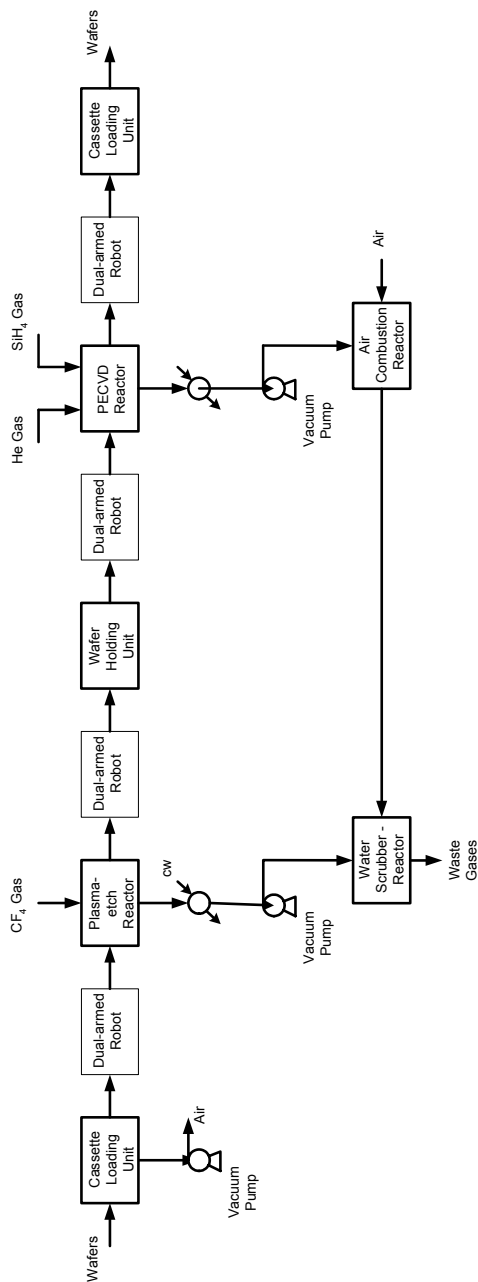


Figure 10.5-1. Flowsheet of manufacturing process

Step 7. The robot transfers the wafer in 20 s to the final cassette-loading unit, which is identical to the initial one. Then, after the unit is filled with 25 cassettes, a machine (not shown) transfers them to a cassette, where they are returned to 1 atm, prior to storing the product wafers.

Note that, with the exception of the PECVD reactors, all of the processing units are commercially available. Furthermore, PECVD reactors similar to the optimal designs determined by Brass and Lee [5] are commercially available, as well. In Table 10.5-1, price quotations from vendors are provided, together with estimates of the clean room area required.

Table 10.5-1: Clean room area estimates and price quotations from vendors

Processing Unit	Clean Room Area, ft ²	Purchase Cost
Dual-armed robot	35.1	\$ 900,000
Plasma-etch reactor	15.9	1,800,000
2 PECVD reactors	15.9	3,600,000
2 Cassette loading units	5.0	2,000
Wafer holding unit	2.5	1,000
Miscellaneous items	20.0	
2 Heat exchangers		9,500
3 Vacuum pumps		51,600
Water scrubber – reactor		100,000
Air combustion reactor		28,000
TOTAL	110.3	\$ 6,492,100

Including 20 ft² for miscellaneous items not identified in this section, 110.3 ft² must be rented, at an annual cost of \$44,100/yr. Note that this moderately sized complex is added to an existing electronic materials manufacturing facility. Hence, no direct charges are added for infrastructure, such as non-clean room and office space. The total purchase cost, \$6,492,100, provides equipment modules that require small installation costs, on the order of 1%; that is, \$65,000. Note also that two PECVD reactors are provided to assure uninterrupted operation when the plant is in operation, around the clock, 330 day/yr. While the robot loads and unloads one of the reactors, the other reactor is in operation.

10.6 ECONOMICS – PROFITABILITY ANALYSIS

The manufacturing facility is designed for a moderately sized business with a single assembly line, providing a small fraction of the epitaxial silicon wafers produced worldwide. Since wafer technology is improving rapidly, the plant is assumed to operate for just seven years, after which it will be replaced by a modern facility. One year of engineering, installation, and startup time is provided. Working capital is invested just prior to the beginning of operation, and is recovered at the end of the seventh operating year. Furthermore, it is assumed that the facility achieves a maximum of 90% capacity during the seven operating years. During the first year, only half of 90% is achieved and, during the second year, three-quarters of 90% is achieved. During years 3-7, 90% of capacity is achieved. Note that at 100% of capacity, operating 330 day/yr, and at 62 s/wafer deposition time, 459,800 wafer/yr are produced. No inflation is assumed.

10.6.1 Investment

After installation, the total cost of equipment (direct permanent investment) is \$6,557,000. Allowing 18% for the cost of contingencies and contractor fees (\$1,180,300), the total depreciable capital is estimated to be \$7,737,000. Ten percent of this is assumed to cover the cost of startup, \$773,700, giving a total permanent investment of \$8,511,000. Working capital is estimated to cover accounts receivable; that is, the sales of 30 days production of wafers (41,800 wafers), assumed to sell for \$260/wafer, giving \$10,868,000. Together with a 2-day inventory of wafers, valued at the product price, the total working capital is \$11,520,000. Hence, the total capital investment is \$20,031,000.

10.6.2 Variable Operating Costs

These costs, which depend upon production rates, include the costs of raw materials, utilities, and general expenses. The dominant cost, to which the total variable cost is closely related, is the price of the 30-cm wafers, polished on both sides. Given a quote of \$206/wafer from Silicon Quest International, the annual cost of purchasing 459,800 wafers is \$94,720,000. For each wafer, 72.9 sccm of silane, 656 sccm of helium, and 32.3 sccm of CF_4 are consumed. At prices of 1.06×10^{-3} , 3.48×10^{-5} , and 1.15×10^{-4} \$/sccm, the costs of these gases are just \$17,500/yr, \$10,500/yr, and \$1,700/yr. Cooling water and electricity requirements are 753 gal/wafer (at \$0.33/1,000 gal) and 16.3 KW-hr/wafer (\$0.035/KW-hr); that is, \$115,000/yr and \$262,100/yr. In addition, general expenses (for research, administration, and management incentives) total \$13,810,000/yr, giving total variable operating costs at 100% capacity of \$108,900,000/yr.

10.6.3 Fixed Operating Costs

These are the costs for operations, maintenance, operating overhead, and property insurance and taxes, costs that are independent of throughput. For operations, 3 operators are assumed over five 40 hr shifts/wk, at a cost of \$18/operator-hr, giving \$561,600/yr. When adding direct salaries and benefits (\$84,200/yr), and operating supplies and services (\$33,700/yr), \$680,000/yr are estimated for operations. To these, estimates of maintenance (\$800,800/yr), operating overheads (\$246,500/yr), and property insurance and taxes (\$246,500/yr) are added, to give a total fixed cost of \$1,882,000/yr.

10.6.4 Cash Flows and Profitability Analysis

Using a \$260/wafer sales price for epitaxial silicon wafers and the United States MACRS tax-basis depreciation schedule, the investor's rate of return (IRR) is 18.3%. In addition, the return on investment (ROI) is 25.3%. These measures increase significantly with small changes in sales price; for example, at \$273/wafer, the IRR is 29.9%. Note that the economic analysis is somewhat shielded from variations in the price of epitaxial wafers because it is strongly linked to the price of the incoming polished wafers. In other words, the key metric of interest is the value added to the wafer by the epitaxial film deposition.

10.7 CONCLUSIONS

For epitaxial silicon wafers, product design focuses on optimizing the geometry of the plasma-enhanced, chemical-vapor-deposition (PECVD) reactor. To increase productivity, and maintain acceptable thickness uniformity, on the order of 5%, a simple optimization strategy locates a design that completes the deposition in 62 s. Then, for a standard manufacturing process, the economics are driven by the wafer costs, which are provided by a vendor at \$206/wafer. At a sales price of \$260/epitaxial wafer, the investor's rate of return is 18.3% and the return on investment is 25.3%.

ACKNOWLEDGEMENTS

This case study is based upon the senior design report by Brass and Lee [5], which was prepared at the University of Pennsylvania in the Spring 2003. The design problem statement was formulated by the first author, who served as the faculty advisor.

REFERENCE

1. R. G. Cooper, *Winning at New Products: Accelerating the Process from Idea to Finish*, Third Ed., Perseus Publ., Cambridge, Mass., 2001.
2. R. G. Cooper, *Product Leadership: Creating and Launching Superior New Products*, Third Ed., Perseus Publ., Cambridge, Mass., 2002.
3. W. D. Seider, J. D. Seader and D. R. Lewin, *Product and Process Design Principles: Synthesis, Analysis, and Evaluation*, Second Ed., Wiley, 2004.
4. A. Armaou and P. D. Christofides, *Chem. Eng. Sci.*, 54 (1999) 3305.
5. D. A. Brass and A. G. Lee, *The Production of Epitaxial Silicon Wafers via Plasma Enhanced Chemical Vaposition*, Univ. Pennsylvania, Towne Library, 2003.

Chapter 11

Design of Industrial Catalysts

Kurt A. Christensen

Haldor Topsøe A/S, Nymøllevej 55, Lyngby, DK-2800, Denmark

11.1 Introduction

Catalysts have been used in industry for more than a century, and today over 90% of the chemical manufacturing processes in use throughout the world utilize catalysts in one form or another. Catalysts play important roles in the production of bulk chemicals such as sulphuric acid, ammonia, nitric acid and methanol, and catalysis is essential in hydrocarbon processing such as hydrocracking, hydrodesulphurization, and catalytic reforming. The desire to reduce production cost and energy consumption in industry has been a major driving force for the development of new catalysts and catalytic processes, and in the past decades an increased focus on environmental protection has called for new catalysts for removal of SO₂, NO_x and organic compounds from off-gases in the chemical industry, from power plants, refineries and from auto-exhaust.

Most industrial catalysts are heterogeneous catalysts consisting of solid active components dispersed on the internal surface of an inorganic porous support. The active phases may consist of metals or oxides, and the support (also denoted the carrier) is typically composed of small oxidic structures with a surface area ranging from a few to several hundred m²/g. Catalysts for fixed bed reactors are typically produced as shaped pellets of mm to cm size or as monoliths with mm large gas channels. A catalyst may be useful for its *activity* referring to the rate at which it causes the reaction to approach chemical equilibrium, and for its *selectivity* which is a measure of the extent to which it accelerates the reaction to form the desired product when multiple products are possible [1].

This chapter discusses the steps involved in the development and design of a new SO₂ oxidation catalyst VK69, which was introduced to the market in 1996 by Haldor Topsøe. The strategy and many of the methods are generally applicable to heterogeneous fixed bed catalysts, partly to fluid and slurry bed catalysts, and less relevant for homogeneous catalysts as found in organic synthesis and enzymatic reactions.

The production of sulphuric acid by the contact process, introduced in about 1875, was the first process of industrial significance to utilize heterogeneous catalysts. In this process, SO₂ was oxidized on a platinum catalyst to SO₃, which was subsequently absorbed in aqueous sulphuric acid. Later, the platinum catalyst was superseded by a catalyst containing vanadium oxide and alkali-metal sulphates on a silica carrier, which was cheaper and less prone to poisoning. Further development of the vanadium catalysts over the last decades has led to highly optimized modern sulphuric acid catalysts, which are all based on the vanadium-alkali sulphate system.

11.1.1 Production of Sulphuric Acid

Sulphuric acid is the largest volume chemical in the world with an annual production of about 180 mill. t/year which is used primarily for phosphate fertilizers, petroleum alkylation, copper ore leaching and in smaller quantities for a number of other purposes (pulp and paper, other acids, aluminium, titanium dioxide, plastics, synthetic fibres, dyestuffs, sulphonation etc.). The major sulphur sources for sulphuric acid production are sulphur recovered from hydrocarbon processing in the refineries and from desulphurisation of natural gas, SO₂ from metallurgical smelter operations, spent alkylation acid, and to a minor extent mined elemental sulphur and pyrites. A simplified flow sheet of a modern double-absorption plant for sulphuric acid production from sulphur is shown in Fig. 1.

Sulphur is combusted with dry air at about 1100°C to a gas with typically 10-12% SO₂ and 9-11% O₂. The gas is cooled in a steam boiler to 380-440°C and passed to the converter, where SO₂ is oxidised to SO₃ according to the reversible exothermic reaction



over typically 4 adiabatic fixed beds loaded with sulphuric acid catalyst pellets. Due to the unfavourable position of the equilibrium at high temperature, the gas is cooled in steam superheaters or heat exchangers between the beds.

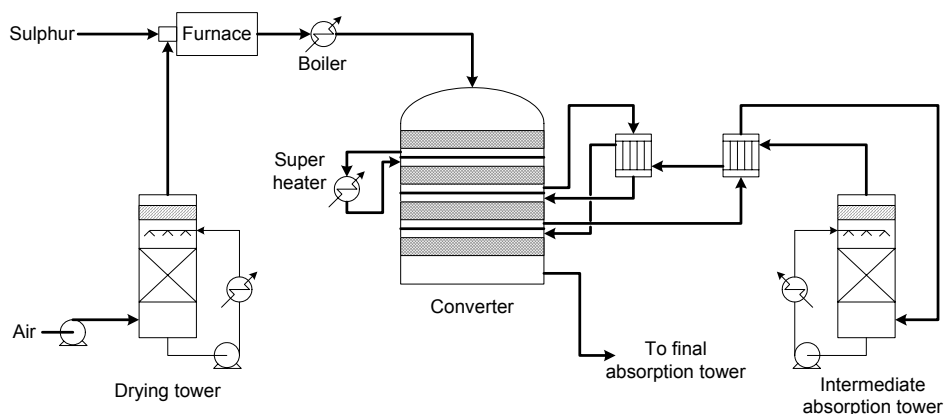


Figure 1. Simplified flow sheet for a sulphur-burning double-absorption sulphuric acid plant (3+1 layout).

Downstream from the 3rd bed, the gas is cooled and passed to an intermediate absorption tower, in which the SO_3 formed is absorbed in recirculating sulphuric acid. The cold and practically SO_3 -free process gas is reheated to 380–440°C and returned to the converter, where the remaining SO_2 is converted to SO_3 in a 4th catalyst bed. The rest of the SO_3 is subsequently recovered in a final absorption tower before the process gas, containing a small fraction of unconverted SO_2 , is emitted through the stack. The combustion air is dried with the 98 wt% product acid in order to avoid corrosion and acid mist problems in the plant. The sulphuric acid process normally operates close to atmospheric pressure with the combustion air blower dimensioned just for compensation of the pressure drop through the plant.

Due to the exothermic nature of reaction (1), the temperature increases through each bed of the converter as SO_2 conversion progresses, cf. Fig. 2. The extent of interbed gas cooling is a compromise between a high approach to equilibrium and a high reaction temperature, both of which will require less catalyst volume. The intermediate absorption enables a total conversion of 99.7–99.9% compared to 97–99% for single absorption plants, dependent on the 4th bed inlet temperature. The layout of plants for processing of smelter off-gases is somewhat different but the converter part is similar to that of the sulphur-burning plant.

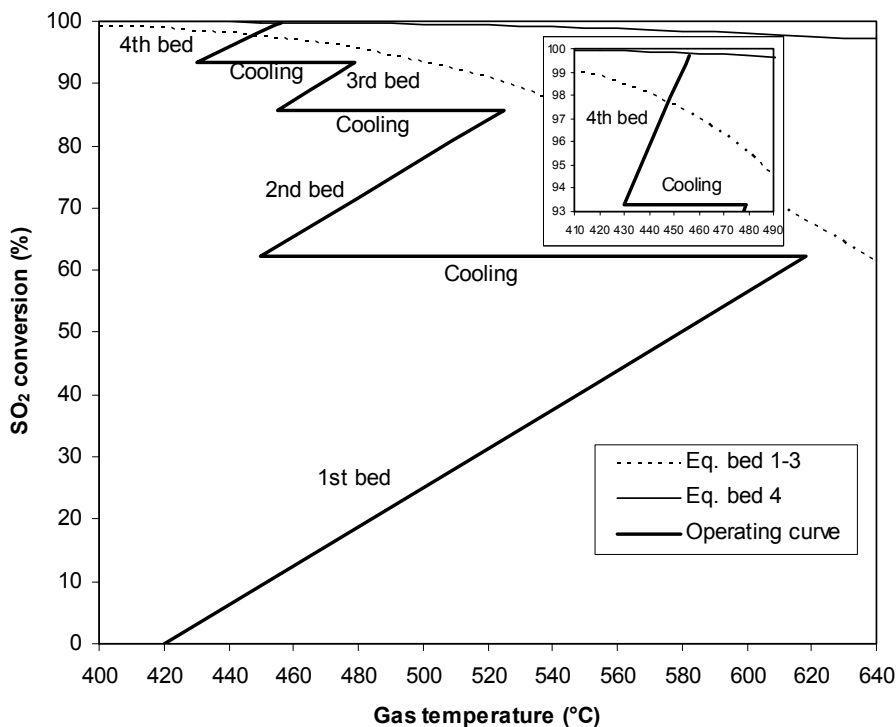


Figure 2. Operating and equilibrium curves showing the total SO₂ conversion for a 4-bed SO₂ converter (3+1 layout) with intermediate absorption of SO₃ downstream bed 3 and conventional catalyst in bed 4. The feed gas contains 11% SO₂ and 10% O₂.

Commercial sulphuric acid catalysts are based on V₂O₅ dissolved in alkali-metal pyrosulphates on an inactive porous silica support. The carrier is usually made from diatomaceous earth, and the catalyst typically contains 2-5 wt% vanadium and 2-5 mole alkali metal promoter per mole vanadium. The alkali promoter is mainly potassium but sodium and caesium are also used in some catalysts. The catalysts are available as cylindrical pellets, cylindrical rings or finned rings resembling a Daisy or a star as shown in Fig. 3. Generally, in the range of 0.15-0.20 m³ catalyst is required per ton H₂SO₄ produced per day depending on the actual feed gas, and the service life of the catalyst is typically 5-8 years for 1st and 2nd bed catalyst and above 10 years for 3rd and 4th bed catalyst.

One of the main drivers for the development of new sulphuric acid catalysts over the last decades has been the desire to reduce SO₂ emissions from sulphuric acid plants without costly tail gas cleaning or an additional interbed

absorption step, which would require high investment cost and reduce the energy efficiency of the process. Because of the unfavourable position of the equilibrium at high temperature, this task addresses a serious limitation of the vanadium-potassium-based sulphuric acid catalyst, being a drastic decrease of activity below 400-430°C.

This chapter describes the background, the strategy and the methods used at Haldor Topsøe in the 1990ies to develop and design a new commercial low-temperature sulphuric acid catalyst called VK69.



Figure 3. The five variants of size and shape of sulphuric acid catalysts from Haldor Topsøe.

11.2 Design of a New Sulphuric Acid Catalyst

The background for the development of VK69 was a need for reduction of SO₂ emissions from double-absorption plants by installing a more active catalyst at low temperature downstream from the intermediate absorption tower. Clearly, the catalytic solution should be more competitive than the alternatives, e.g. tail gas scrubbing or triple-absorption layout, in terms of capital and operating costs. In the following, the required technical performance of the catalyst with respect to SO₂ oxidation activity, mechanical strength and pressure drop is discussed, and input from the literature and from practical experience in the field is presented. Reviews of the extensive literature published on sulphuric acid catalysts can be found in [2-5].

11.2.1 Catalyst Activity

The activity, which may be defined as the net rate of SO_2 oxidation in moles/s/m^3 catalyst according to reaction (1), depends on the intrinsic activity of the catalyst material, the diffusion properties of the catalyst material, the size of the catalyst pellets, and the shape of the pellets.

As a starting point, we will try to quantify the required activity of a new catalyst by simulating the SO_2 emission from a double absorption plant as a function of 4th bed catalyst activity for a feed gas with 11% SO_2 and 10% O_2 and a 3+1 converter with fixed bed volumes, cf. Fig. 4. With a conventional potassium-promoted catalyst such as VK38 from Haldor Topsøe (relative activity 1), a typical requirement in the 1990ies of minimum 99.7% SO_2 conversion corresponding to 395 ppm SO_2 in the stack gas can be achieved in this plant at a 4th bed inlet temperature of 430-435°C. With a 2-3 times more active catalyst in bed 4, the SO_2 emission in this plant can be reduced to below 200 ppm at a lower optimum inlet temperature.

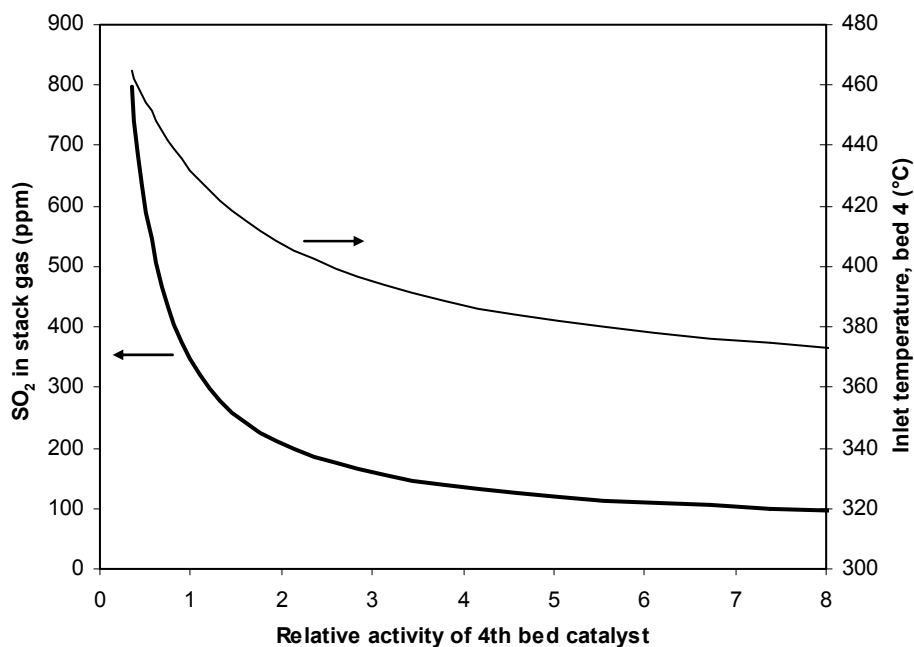


Figure 4. The SO_2 concentration in the stack gas and the optimum 4th bed inlet temperature as a function of 4th bed catalyst activity for a 3+1 double absorption plant with fixed catalyst volume in bed 4.

Sulphuric acid catalysts are not truly heterogeneous catalysts but so-called supported liquid phase (SLP) catalysts, where the oxidation of SO_2 takes place as a homogeneous reaction in a liquid film covering the internal surface of the support material [2]. This was proposed already in 1940 by Frazer and Kirkpatrick [6], who found that the promoting action of the common alkali metals was due to their ability to form relatively low-melting pyrosulphates, which dissolve vanadium oxides, e.g. for potassium



The catalytic activity of the melt was later demonstrated conclusively by Topsøe and Nielsen [7], who obtained a high degree of conversion to SO_3 by bubbling SO_2 and oxygen through a column packed with raschig rings and containing molten potassium pyrosulphate in which 14% wt% V_2O_5 was dissolved. They also prepared catalysts with different alkali metals and concluded that higher activity was obtained if K was exchanged by heavier alkali metals (Cs or Rb) due to their ability to absorb more SO_3 than corresponding to pyrosulphate.

Since then numerous investigations on the co-ordination chemistry of the catalytic melt and the reaction mechanism have been published, but in spite of this the details of the mechanism are still unknown. For many years, the mechanism was assumed to include reduction of vanadium to V^{4+} and reoxidation to V^{5+} by oxygen as proposed by among others Mars and Maessen [8], but in recent years only V^{5+} is believed to be active in the catalytic cycle [5].

However, V^{4+} compounds still play an important role for the activity of the catalyst because an equilibrium exists between V^{5+} and V^{4+} compounds in the melt. The degree of reduction to inactive V^{4+} increases at low temperature and high SO_2 partial pressure, and it has also been found to depend on the liquid dispersion on the support [9]. Furthermore, at temperatures below 500°C some V^{4+} compound precipitates and gradually depletes the melt of V^{5+} when the temperature is lowered, and this partial solidification eventually causes the activity to drop to practically zero at some minimum operating temperature of about 350°C .

Another important parameter is the liquid loading defined as the fraction of the pore volume of the support filled with melt. The activity of a catalyst increases proportional to the liquid loading (which is proportional to the vanadium

content) at low loadings but decreases at high loading due to gas phase pore diffusion restriction and liquid diffusion restriction in the deeper melt pools [10]. As a consequence, an optimum melt loading exists for a given melt composition and operating conditions.

The silica carrier of a sulphuric acid catalyst, which has a relatively low surface area, serves as an inert support for the melt. It must be chemically resistant to the very corrosive pyrosulphate melt and the pore structure of the carrier should be designed for optimum melt distribution and minimum pore diffusion restriction. Diatomaceous earth or synthetic silica may be used as the silica raw material for carrier production. The diatomaceous earth, which is also referred to as diatomite or kieselguhr, is a siliceous, sedimentary rock consisting principally of the fossilised skeletal remains of the diatom, which is a unicellular aquatic plant related to the algae. The supports made from diatomaceous earth, which may be pretreated by calcination or flux-calcination, exhibit bimodal pore size distributions due to the microstructure of the skeletons, cf. Fig. 5.

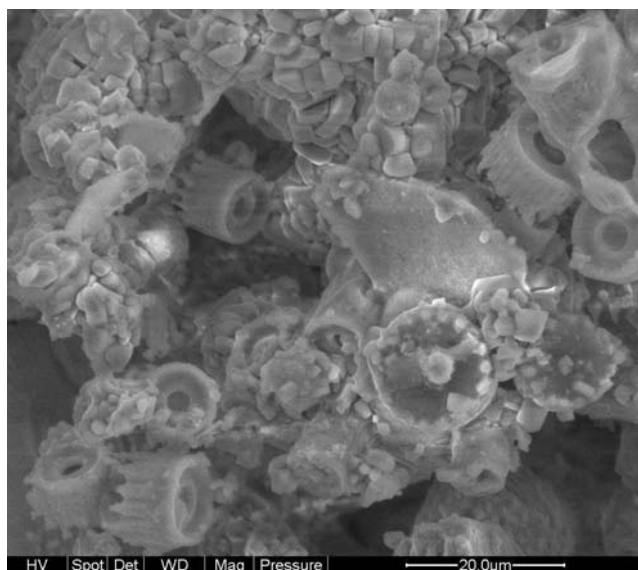


Figure 5. Scanning Electron Micrograph of the interior of a sulphuric acid catalyst. Diatom skeletal fractions more or less covered with solidified catalytic melt are discernible.

The principal idea in the development of VK69 was to use caesium as a low-temperature promoter in a vanadium-based catalyst designed specifically for operation in the beds downstream from the intermediate absorption tower. The company had already gained a lot of experience with Cs in sulphuric acid catalysts because the first Cs-promoted catalyst in the market, VK58, had been introduced back in 1988 by Haldor Topsøe. VK58 was designed primarily for operation in strong gases in the 1st bed and in the final bed of single absorption plants. At that time the available caesium raw material had to be pretreated in the production facility to produce a suitable water-soluble intermediate, but when the VK69 development was initiated, a stable market for water-soluble Cs salts had developed. The complicated chemistry of the vanadium-alkali-metal pyrosulphate catalyst, which is still far from understood, calls for a high degree of empirical development of the chemical composition of the catalyst.

The catalyst activity depends not only on the chemical composition but also on the diffusion properties of the catalyst material and on the size and shape of the catalyst pellets because transport limitations through the gas boundary layer around the pellets and through the porous material reduce the overall reaction rate. The influence of gas film restrictions, which depends on the pellet size and gas velocity, is usually low in sulphuric acid converters. The effective diffusivity in the catalyst depends on the porosity, the pore size distribution, and the tortuosity of the pore system. It may be improved in the design of the carrier by e.g. increasing the porosity or the pore size, but usually such improvements will also lead to a reduction of mechanical strength. The effect of transport restrictions is normally expressed as an effectiveness factor η defined as the ratio between observed reaction rate for a catalyst pellet and the intrinsic reaction rate, i.e. the hypothetical reaction rate if bulk or surface conditions (temperature, pressure, concentrations) prevailed throughout the pellet [11]. For particles with the same intrinsic reaction rate and the same pore system, the surface effectiveness factor only depends on an equivalent particle diameter given by

$$d_{eq} = 6 \cdot \frac{V_p}{A_p} \quad (3)$$

where A_p is the external surface area and V_p the volume of the particle. A calculation of the effectiveness factors for a conventional catalyst without caesium in the 4th bed of a 3+1 converter as a function of d_{eq} shows the benefit of small catalyst particles under this condition (Fig. 6). For a more active catalyst material than that in Fig. 6, the effectiveness factor will be lower for the same d_{eq} . For very active catalyst systems, the active components can be utilized more efficiently by shell-impregnation or as monoliths, but this was not considered advantageous for VK69.

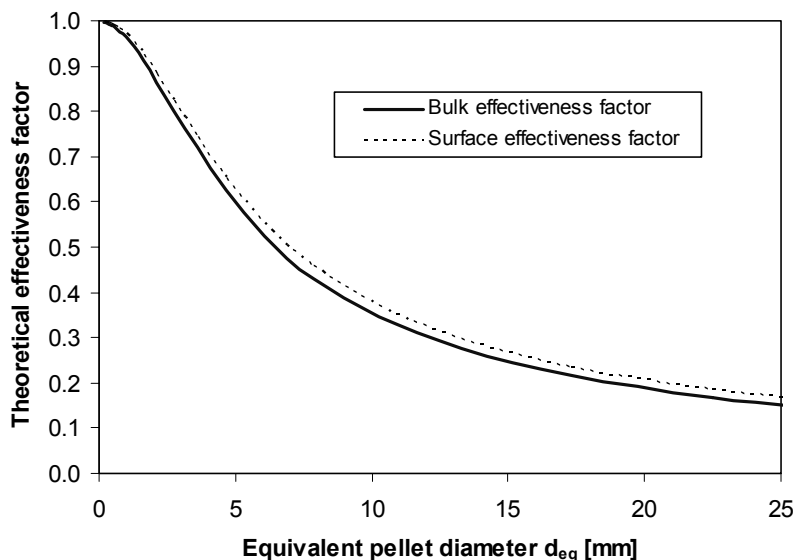


Figure 6. Effectiveness factor for SO_2 oxidation over VK38 in 0.7% SO_2 and 7% O_2 at 400°C.

Another important constraint especially for existing industrial converters is the volume available in the reactor for the catalyst. Accordingly, the reaction rate per unit bed volume

$$r_{\text{SO}_2, \text{bed}} = (1 - \varepsilon) \cdot r_{\text{SO}_2, \text{pellet}} = \eta_b \cdot (1 - \varepsilon) \cdot r_{\text{SO}_2, \text{intrinsic}} \quad (4)$$

must be considered. A very open-structured catalyst, e.g. a thin-walled monolith, with a high bed void fraction ε may have a high effectiveness factor but a much higher reactor volume will be required to provide the same total conversion. Likewise, small pellets providing a high effectiveness factor will lead to a high pressure drop across the catalyst bed which can be unacceptable (cf. section 2.3 below).

11.2.2 Mechanical Strength

The mechanical strength of a catalyst is essential for maintaining low pressure drop over the converter. The first requirement is a low fractional break-up during handling, transportation and loading in the converter, where the pellets

fall from a height of typically 0.5-1.5 m. Furthermore, the pellets must be able to resist the forces imposed on the catalyst in a fixed bed including the weight of catalyst above, the force applied by the pressure drop, and the movement due to thermal expansion of the converter at varying temperatures. Finally, the pellets will experience pneumatic transport because sulphuric acid catalyst beds are normally screened regularly in order to remove dust accumulated in the bed from the synthesis gas. Prediction of screening loss of a new catalyst is complicated by the fact that the pellet strength depends on the history of operating conditions experienced by the catalyst in the converter.

In addition to the external forces, the catalyst must also resist internal forces imposed on the pellet as phase transitions in the catalyst material progress. These transitions, including e.g. transformation of the amorphous silica carrier into crystalline α -cristobalite, precipitation of V^{4+} and V^{3+} compounds, and destruction of the carrier by the melt, may eventually cause the catalyst to break up in smaller particles or even to catalyst powder.

The catalyst strength is generally improved at low porosity but this usually causes an adverse effect on the activity. Due to the low operating temperature and low SO_2 concentration, the conditions for the new catalyst in a 4th bed are not as severe as in the upper beds.

11.2.3 Pressure Drop

The desire to save energy calls for low pressure drop over the catalyst layers because they account for a significant part of the total pressure drop through the sulphuric acid plant. According to simple correlations such as the Ergun equation [12], the pressure drop over a catalyst bed per bed length at a given flow rate and properties of the gas only depends on the bed void fraction ε and a characteristic pellet diameter

$$\Delta P = k \cdot \frac{1}{d_{eq}} \cdot \frac{1 - \varepsilon}{\varepsilon^3} \quad (5)$$

where k is a proportionality constant and d_{eq} is given by (3). For a reaction rate controlled by pore diffusion, the pellet reaction rate is inversely proportional to d_{eq} , and as a consequence of (5) the ratio of catalyst activity to pressure drop is independent of pellet size for fixed geometrical shape in this case. In practice it must be taken into account that the void fraction depends both on industrial loading procedure and on the distribution of pellet lengths from the extrusion process.

11.2.4 Production

In principle, any catalyst developed in the laboratory can be manufactured in large scale. In practice, however, the necessary investments, which may include development of the production process, and the operating costs of the catalyst production plant including availability and cost of raw materials, plant maintenance, labour etc. may not be justified by the market potential. In the VK69 case, production in the existing plant according to the route in Fig. 8 was preferred but not a strict requirement.

11.3 Design Strategy

The development and design of the new sulphuric acid catalyst involves numerous disciplines, work tasks and methods from the field of practical catalysis and chemical engineering. The most important steps of the development process are briefly described in this section but for a deeper technical approach to the theory and methods, the reader is referred to text books within the field [1, 13-14].

The starting point for a route to a new commercial catalyst is typically new market opportunities or requirements to performance identified in a competitive market, cf. Fig. 7. However, ideas fostered from observations in the laboratory or elsewhere in an organisation may also be recognised as a source of new product opportunities. In the first stages of the catalyst development, formulation with different carriers, shapes, compositions and calcinations are tested with respect to catalytic activity, mechanical strength and pressure drop. In the later stages of the development, full-scale production is demonstrated, the catalyst stability and durability are validated and detailed performance data are acquired. An innovative attitude is important especially in the first stages of development, where different catalyst formulations are proposed and selected, but in all steps of the testing much can be learned from the experimental observations. In the evaluation steps shown in Fig. 7, the profitability of the catalysts is compared based on the measured performance, estimated production cost and market analyses. However, the profitability should be taken into account throughout the development process in order to avoid e.g. exotic production routes or expensive raw materials that will fail to pass the evaluations anyway. In this way, the work on non-competitive products can be stopped early in the process. The individual tasks and methods used for the development of VK69 are described in the following and a selection of results are presented and discussed in the next section.

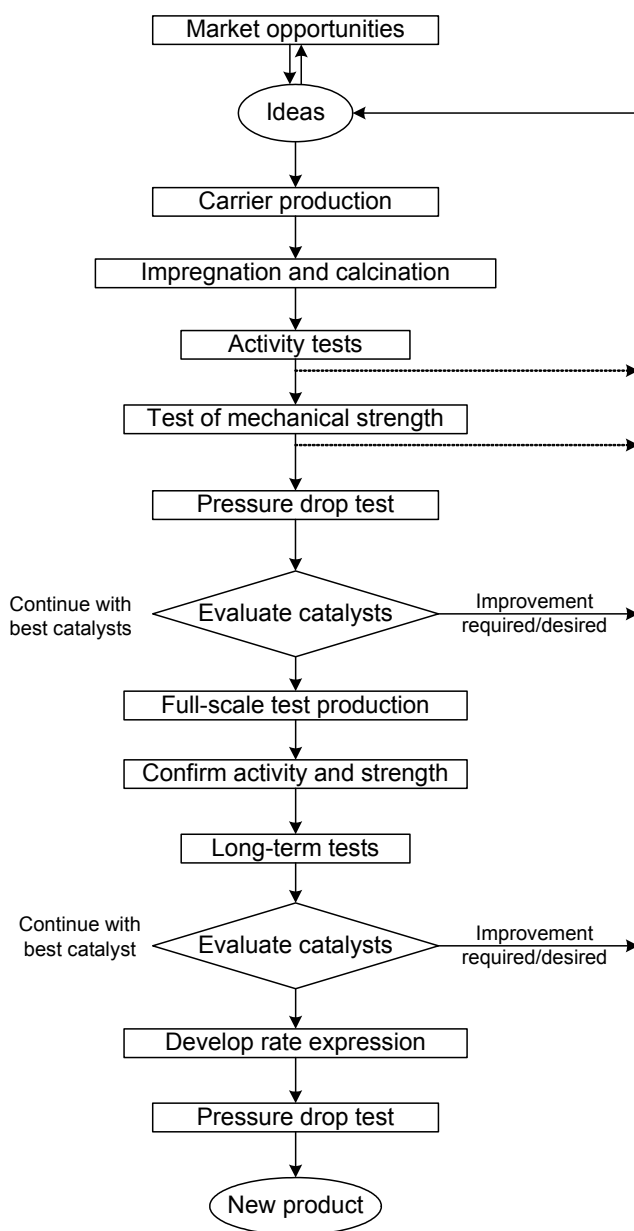


Figure 7. Strategy for design of a new sulphuric acid catalyst.

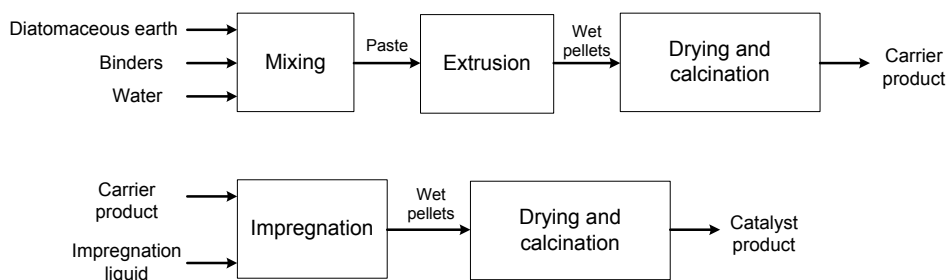


Figure 8. Simplified diagram of unit operation in the production of sulphuric acid catalyst.

11.3.1 Production of Carrier

The first task was to produce carriers from different recipes and in different shapes as shown schematically in Fig. 8. The raw materials diatomaceous earth, water and various binders are mixed to a paste, which is subsequently extruded through a shaped nozzle and cut off to wet pellets. The wet pellets are finally dried and heated in a furnace in an oxidising atmosphere (calcination). The nozzle geometry determines the cross section of the pellet (cf. Fig. 3) and the pellet length is controlled by adjusting the cut-off device. Important parameters in the extrusion process are the dry matter content and the viscosity of the paste. The pore volume distribution of the carriers is measured by Hg porosimetry, in which the penetration of Hg into the pores of the carrier is measured as a function of applied pressure, and the surface area is measured by the BET method, which is based on adsorption of nitrogen on the carrier surface [1].

11.3.2 Impregnation and Calcination

The carriers were impregnated to different compositions in terms of vanadium content, K/V ratio, Na/V ratio, Cs/V ratio and sulphur content, cf. Fig. 8. The exact sulphur content is less important since the melt, according to reaction (2), takes up an equilibrium amount of SO_3 corresponding to a sulphur to alkali metal molar ratio of about 1 during operation in synthesis gas. The impregnation was carried out by submerging the pellets for a period of time in a surplus of aqueous impregnation liquid prepared from sulphuric acid and water-

soluble salts of V and alkali promoters K, Na, and Cs. In this step, the liquid is sucked into the pores of the carrier due to capillary forces and the final catalyst composition is determined by the porosity of the carrier and the concentrations in the impregnation liquid. The wet pellets were finally dried and calcinated by heating in a furnace in an oxidising atmosphere.

The catalyst samples produced as described above were subsequently analyzed and tested in the laboratory with respect to catalytic activity, mechanical strength and pressure drop.

11.3.3 Activity Test

Because the composition and nano-scale structure of a catalyst depend on the temperature and the gas environment, it is important to measure catalyst activity under conditions experienced in the industrial converters. For the sulphuric acid catalysts, the activity for conversion of SO_2 to SO_3 was measured in the set-up shown in Fig. 9.

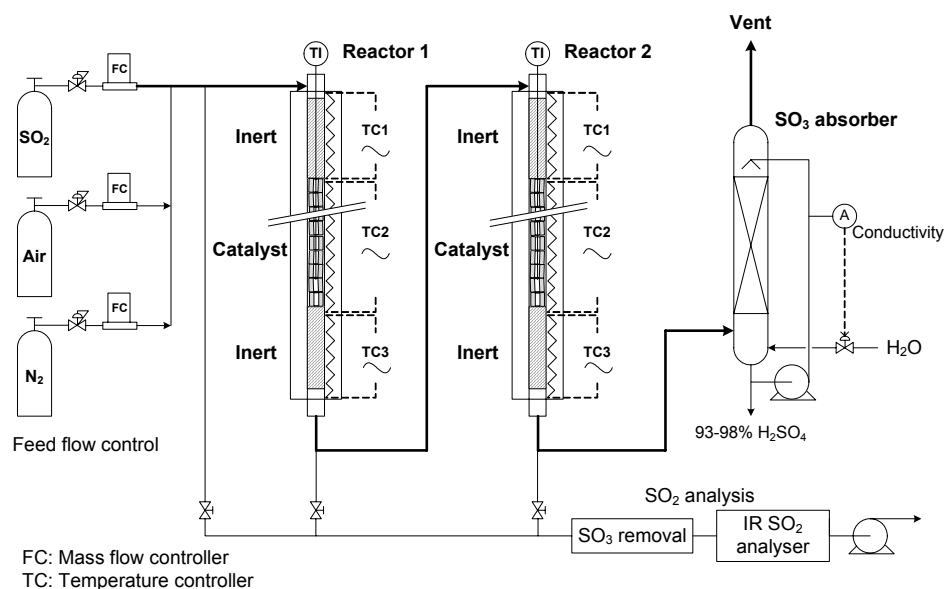


Figure 9. Experimental unit for measurement of catalytic SO_2 oxidation activity.

A dry feed gas is mixed from SO_2 , air and nitrogen to a total flow of 50-200 Nl/h with typically 0.2-20 % SO_2 and 3-20 % O_2 . For wet gases or O_2 -enriched conditions, water vapour and oxygen can also be added to the feed gas. The conversion of SO_2 over the catalyst is measured in one or more isothermal integral fixed bed reactors connected in series and operating typically at 300-750°C with 10-90% incremental SO_2 conversion in each reactor (2 reactors are shown in the figure). Isothermal conditions in the catalyst bed are achieved by controlling the output to the three heater zones of the reactor oven. The effluent gas from the final reactor is passed to an SO_3 absorber, since the SO_3 would otherwise produce sulphuric acid mist in the environment when mixed with humid air. The SO_3 is absorbed in recirculating concentrated sulphuric acid, the concentration of which is automatically controlled by conductivity measurement. The conversions are determined by an IR SO_2 analyser as shown in the figure or by titration with iodine (Reich method). Because isothermal measurements do not follow the adiabatic reaction lines shown in Fig. 2, several measurements at different temperature and conversion levels may be necessary to adequately cover the conditions through an industrial adiabatic bed.

Various test reactors are available for the measurement of catalytic activity (adiabatic integral reactors, isothermal integral reactors, differential recirculation reactors, Carberry reactors, Berty reactors etc.), and the catalyst loading can be designed to measure the activity of whole pellets or intrinsic activity (small particles). The reactors used in the present case are so-called single pellet string reactors (SPS), in which a number of whole pellets are stacked on top of each other in a single row in a reactor tube at isothermal conditions. This reactor type, which has previously been investigated for reaction between pelletized iron ores and gases [15], has been adopted and perfected by Haldor Topsøe for catalyst activity measurements. For sulphuric acid catalysts, we have found that the SPS reactor is an excellent approximation to large scale adiabatic reactors while maintaining the advantages of small-scale units, e.g. the ability to operate isothermally, quick response and ease of operation. The advantage of using whole pellets is that the measured reaction rate includes all effects of transport and inhomogeneities inside the pellet and hence no additional uncertainty is introduced from interpretation of internal transport restrictions. Catalyst samples may directly be ranked according to measured conversions under equal conditions, but further quantification requires some reaction rate model because the integral conversion is measured. For other catalyst systems involving a very active catalyst or a very high heat production in the pellet, external transport restrictions are more important and in this case, more attention must be paid to correcting for differences in mass and heat transfer coefficients between the SPS reactor and industrial reactors.

The initial screening of VK69 catalyst samples was carried out at 380-420°C in 0.7% SO₂ and 7% O₂ which is a typical 4th bed condition in a 3+1 double absorption plant. A lot of the samples, however, were also tested under other conditions partly to test their performance in a broader range, e.g. 3rd bed in a 2+2 layout, and partly to keep an eye open for beneficial effects of the formulation not detected at the reference conditions. The initial testing also provided information about catalyst stability. In general, the measurements are preferably based on stable activity but some catalyst systems deactivate to a stable level during initial operation while others keep deactivating. If deactivation occurs, it is important to compare the catalysts after equal periods on stream. On the other hand, if the catalyst activity continuously decays during the test, stabilisation of the carrier or the active phases may turn out to be the focal point of the product development.

Based on the activity test results, new experimental series with different impregnations on the same carrier are typically carried out in order to optimise the chemical composition for a given carrier.

11.3.4 Test of Mechanical Strength

Several methods have been used for quantification of mechanical strength of catalysts and carriers since no single method simulates all the requirements mentioned previously. The *attrition loss* is measured by placing a quantity of pellets in a rotating horizontal cylinder. After a number of revolutions, the attrition loss is determined by sieving smaller pieces from the sample. The *bulk crush strength* is measured by slowly forcing a piston down onto a bed of catalyst pellets and measuring the displacement as a function of applied pressure. The *side crush strength* is a measure of the radial force necessary for a piston to crush single pellets. In the *drop test* a number of pellets are dropped individually from a height of 12 m and the number of broken pellets and the weight lost by fragmentation are recorded.

Although the results from these methods may correlate to some extent, they simulate different essential requirements of the catalysts. Attrition loss primarily relates to handling, transport, loading and screening whereas the crush tests simulate the forces imposed on the catalyst in a fixed bed. The drop test simulates the risk of catalyst break-up during loading and pneumatic transport.

When these tests are used for both carrier and catalyst, the catalyst is stronger than the carrier due to the vanadium and alkali salts, which may constitute 30-40% of the catalyst weight. However, the increased strength measured for the

pellets after impregnation cannot be expected truly to represent all aspects of the industrial conditions, because the salts are in a molten state during operation and hence contributes less to the pellet strength.

11.3.5 Test of Pressure Drop

The pressure drop for the produced carrier or catalyst is measured in the setup shown in Fig. 10. An adjustable flow rate of 300-700 Nm³/h ambient air is supplied by a blower and passed downwards through a bed of catalyst in a long tube. The diameter of the bed is 0.39 m, which is well above the minimum of 10 pellet diameters required for satisfactory reproduction of the void fraction observed in a large fixed bed. The catalyst is poured into the tube from the top and the bed may subsequently be settled by applying a reproducible tapping or vibration to the tube. Since the latter reduces the void and increases the pressure drop, it is important that the catalysts are loaded and vibrated in the same way in order to get comparable results. The pressure drop without catalyst should be checked in order not to introduce errors from the support grid or measuring taps.

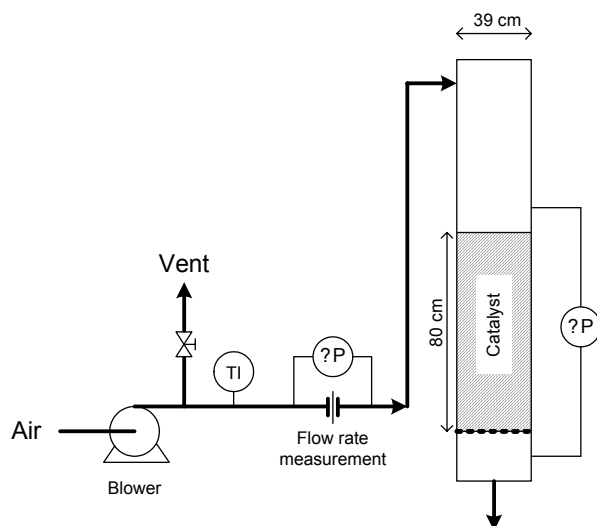


Figure 10. Experimental unit for measurement of pressure drop over a catalyst bed.

The flow pattern is primarily determined by the particle Reynolds number, which is about 100 in the industrial converter (superficial velocity 0.35-0.55 Nm/s), but in order to improve the accuracy of the comparison of different catalysts, higher flow rates are also included. Although theoretical correlations can be used for extrapolating the measured pressure drops for a new shape to the industrial operation temperature, a more reliable method is to calculate the pressure drop from industrial experience for well-known shapes, e.g. 10-mm ring, and assume the same relative pressure drop as in the cold measurements.

11.3.6 Full-scale Test Production

After the evaluation of the performance of the different catalysts prepared in laboratory and pilot scale, a few candidates are selected for a full-scale test production. The main purpose is to demonstrate that the production steps shown in Fig. 8 are feasible for the new catalyst and that a uniform and satisfactory product quality can be achieved at an acceptable production rate in the existing production line.

Normally, the best activities observed during the development process are found for catalysts prepared in the laboratory where special attention is paid to each preparation step and where better control of e.g. impregnation and calcination temperature history can be achieved. This should be kept in mind when comparing activities of new lab-prepared catalysts with standard products from a production facility. As a consequence, it is seldom worth the effort to continue with a test production if the activity of the lab-prepared catalyst fails to meet the requirements. Important results for the test-produced catalysts are activity measurements covering the full range of operating conditions in the industrial converter and the mechanical strength.

In some cases, it may not be possible to produce the new catalyst in an existing production facility due to e.g. limitations of the existing equipment or a need for new unit operations. In this case, a pilot scale production or a full-scale demonstration of the critical steps should be considered before investing in a new production line.

11.3.7 Test of Deactivation

Already in the first activity tests, information on the rate of deactivation is gained because the SO₂ conversion is measured several times during an activity

test running from a couple of days to some weeks until stable activity is observed. However, at some point during the development process, catalyst deactivation and stability must be tested under the relevant operating conditions in a long-term test running for extended periods, e.g. a year. This may be carried out under well-controlled conditions in a dedicated laboratory setup similar to the one in Fig. 9, possibly with reactors connected in parallel with different catalysts. For a more rigorous test, an open canister with the catalyst can be placed in the full depth of an industrial catalyst bed for a year or two and subsequently be analysed in the laboratory. The strength of this test is that the catalyst experiences the industrial gas including impurities such as dust and potential catalyst poisons, and that several start-ups, shut-downs, temperature excursion and concentration variations may be included in the history of the test.

11.3.8 Development of Rate Expression

When the best catalyst has been chosen and found to fulfil the requirements with respect to activity, strength, pressure drop, production and profitability, a procedure must be developed for calculation of the catalyst volume required to obtain a given SO₂ conversion in an industrial reactor. In its simplest form, the calculation basis can be a table or an expression for space velocity (NHSV) as a function of feed gas properties and final conversion. A more detailed approach is used for design of catalytic reactors at Haldor Topsøe, where a rate expression of the form

$$\text{reaction rate} = -r_{\text{SO}_2}(p_{\text{SO}_2}, p_{\text{O}_2}, p_{\text{SO}_3}, P, T) \quad (6)$$

is integrated through the fixed bed by a proprietary reactor simulation tool. The detailed form of r_{SO_2} , which of course must include the correct thermodynamic equilibrium, is developed from activity measurements in the setup shown in Fig. 9.

The pressure drop over the catalyst is measured again with a charge from the test production, since the precise pellet size distribution and settling properties may differ from those of the lab or pilot scale production.

The new catalyst is now ready to be offered to the sulphuric acid industry.

11.4 Results

In the following, a selection of results from the development of VK69 are presented and discussed in order to illustrate the purpose and value of the individual steps of the scheme described above.

Numerous carriers were produced from different recipes and in different sizes and shapes in a 1 kg/min lab scale extruder and subsequently calcinated under different conditions in a furnace. The recipes included different types of diatomaceous earth, different types and amounts of binder and variation of the water content of the paste, which is a critical extrusion parameter. The shapes included among others rings, multiple-holed rings, finned rings, and trilobes, whereas normal cylindrical pellets were not made due to their well-known inferior activity to pressure drop ratio.

11.4.1 Activity Measurements

The carriers were impregnated and calcinated in the laboratory, and the activity was subsequently measured in the set-up shown in Fig. 9. The vanadium content was varied in the range 2-5 wt% and the molar ratios between alkali promoter and vanadium were varied in the ranges 0-4 for K/V, 0-2 for Na/V, and 0-3 for Cs/V. The sulphur content was about the same in all impregnations. The measured activities for 3 catalyst compositions A, B, and C impregnated on the same carrier and with the same vanadium content and molar ratios of K/V and Na/V are given in Table 1. The extrudates are made in the 9 mm Daisy form, which is the special 5-finned ring offered by Haldor Topsøe (Fig. 3). The observed pellet activity is reported as a pseudo-1st order rate constant calculated from

$$k_{1,obs} = -NHSV_{net} \cdot x_{eq} \cdot \ln(1 - x/x_{eq}) \quad (7)$$

where x_{eq} is the equilibrium conversion. According to the table, the Cs-containing catalysts are 61-117% more active than the standard product VK38 in the 12-mm Daisy form. The activity increases with Cs load, but seems to level off at high loadings. About 30% of the activity gain when compared to VK38 is due to the smaller size of the 9-mm Daisy particle.

Table 1. The effect of Cs content on the observed catalyst activity in a feed gas containing 0.7% SO₂ and 7% O₂.

Catalyst composition	A	B	C
Cs/V	low	medium	high
$NHSV_{net}$ (Nm ³ /h/m ³)	13089	14085	13228
Conversion, x	0.5972	0.6639	0.7023
$k_{1,obs}$ (Nm ³ /h/m ³)	11955	15446	16136
$k_{1,obs}/k_{I(VK38, 12\text{ mm})}$	1.61	2.08	2.17

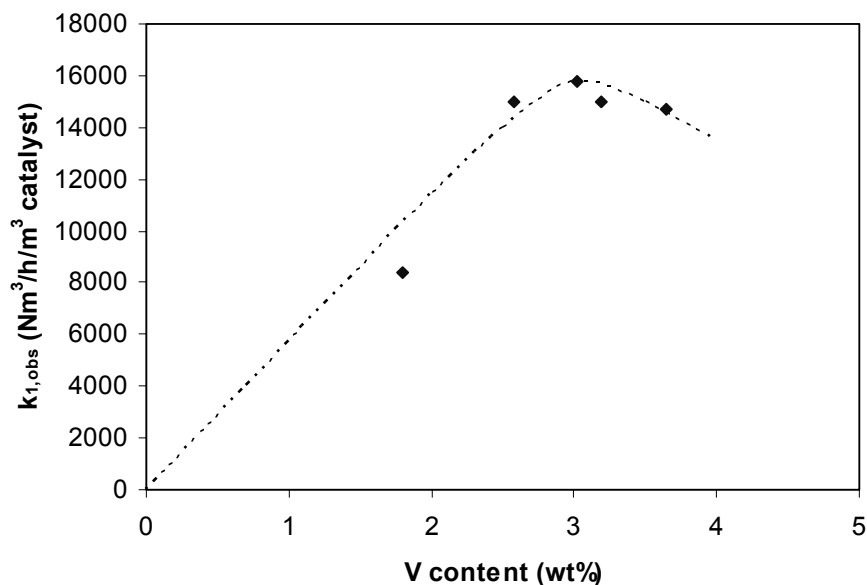


Figure 11. Observed activity of 1-2 mm catalyst particles in 0.7% SO₂ and 7% O₂ as a function of vanadium content for fixed molar ratios of K/V, Na/V, and Cs/V.

The effect of liquid loading was also studied by varying the V content at constant melt composition, i.e. constant ratios of K/V, Na/V, and Cs/V. An example of 1-2 mm large particles depicted in Fig. 11 shows an optimum vanadium content of about 3 wt% for this particular carrier and melt composition.

In order to optimize the size and shape of the catalyst particle, activities for pellets produced from the same material were measured for different sizes and shapes. Some of the results are reported in Table 2. The measured k_1 values show that 9-mm particles are 35% more active than 12-mm particles and that the activity of a 9-mm VK69 is 2.3 times better than a conventional VK38 in the form of a 12-mm Daisy.

The activity calculated from (7) comprises both film and pore diffusion resistance, but also the positive effect of increased temperature of the catalyst particle due to the exothermic reaction. From the observed reaction rates and mass- and heat transfer coefficients, it is found that the effect of external transport restrictions on the reaction rate is less than 5% in both laboratory and industrial plants. Thus, Table 2 shows that smaller catalyst particles are more active due to less diffusion restriction in the porous particle. For the dilute SO_2 gas, this effect can be analyzed by an approximate model assuming 1st order reversible and isothermal reaction. In this case, the surface effectiveness factor is calculated from

$$\eta_s = \frac{1}{\theta} \cdot \left(\frac{1}{\tanh(3\theta)} - \frac{1}{3\theta} \right) \quad (8)$$

with the Thiele modulus given by

$$\theta = \frac{d_{eq}}{6} \sqrt{\frac{k_1}{D_{eff} \cdot x_{eq}}} \quad (9)$$

The activity in terms of 1st order rate constant $k_{1,calc}$ was calculated in Table 2 from (8) and (9) with effective diffusivity $D_{eff}=5.3 \cdot 10^{-6} \text{ m}^2/\text{s}$ and intrinsic rate constant $k_1=33000 \text{ Nm}^3/\text{h}/\text{m}^3 = 23 \text{ s}^{-1}$ fitted to the measurements. This simple and useful method models the measured influence of particle size satisfactorily for a first optimization of particle size and shape. The 35% higher activity measured for the 9-mm Daisy compared to the 12-mm Daisy, however, exceeds the 25% expected from (8), and this illustrates the importance of measuring the activity of the actual shape.

The 1-2 mm particles were prepared by crushing the 9 mm pellets and separating the 1-2 mm particle size fraction by sieving. In this way, the small particles have the same intrinsic properties as the 9 mm pellet. However, consistent results are not always obtained because a larger fraction of the

catalyst volume comes from the interior of a pellet, which is different from the surface layer due to the processes taking place during extrusion, drying and calcination. In order to obtain truly intrinsic activity ($\eta \approx 1$), even smaller particles may be tested, but for very small particles (< about 0.2 mm) channelling and gas bypass may be a problem.

For a more detailed analysis of measured transport restrictions and reaction kinetics, a more complex reactor simulation tool developed at Haldor Topsøe was used. The model used for sulphuric acid catalyst assumes plug flow and integrates differential mass and heat balances through the reactor length [16]. The bulk effectiveness factor for the catalyst pellets is determined by solution of differential equations for catalytic reaction coupled with mass and heat transport through the porous catalyst pellet and with a film model for external transport restrictions. The model was used both for optimization of particle size and development of intrinsic rate expressions. Even more complex models including radial profiles or dynamic terms may also be used when appropriate.

Table 2. The effect of catalyst pellet size on the observed activity of VK69 in feed gas containing 0.7% SO₂ and 7% O₂.

Pellet size	10 mm	12 mm	9 mm	1-2 mm
Shape	Ring	Daisy	Daisy	crushed
d_{eq} (mm)	7.07	6.25	4.68	1.3
$NHSV_{net}$ (Nm ³ /h/m ³)	13053	12771	16393	20080
Conversion, x	0.5813	0.6298	0.6485	0.775
$k_{l,obs}$ (Nm ³ /h/m ³)	11412	12755	17233	30233
$k_{l,obs}/k_l(\text{VK38, 12 mm})$	1.54	1.72	2.32	4.07
θ	2.41	2.13	1.60	0.44
η_s	0.36	0.40	0.50	0.90
$k_{l,calc} = \eta_s \cdot k_l$ (Nm ³ /h/m ³)	11801	13068	16368	29669

11.4.2 Mechanical Strength Results

The mechanical strength of the carriers produced in lab scale (Fig. 8) was quantified in terms of attrition loss, side crush strength and drop test strength. An example of the results is given in Table 3 for carriers D and E prepared with

different amounts of binder in the recipe. Pellets D made with a high amount of binder became more dense with a resulting higher side crush strength and a lower fractional break-up in the drop tests. However, the lower effective diffusivity for the dense pellets also resulted in about 40% lower activity.

In order to compare the strength of different catalyst shapes produced from the same recipe, drop tests were carried out for 10-mm rings and 12-mm Daisy shapes in Table 4. It is evident from the results that Daisy pellets are much more resistant to break-up in the drop test than the rings. The difference may be explained by assuming that the ribbons on the Daisy shape protect the cylinder against breakage. Although the rings are heavier than the Daisy pellets, this seems to be of less importance considering that the falling times are almost the same. It was also observed, that the material in the ribbons was harder than that deeper inside the cylinder and that the ribbons were not even damaged when acting as shock absorbers.

Table 3. Strength test results for two carriers produced as 12 mm Daisy from similar recipes except for the amount of binder.

Carrier recipe	D	E
Amount of binder	high	low
Pellet density (g/ml)	0.74	0.62
Side crush strength (avg. for 10 pellets, N/cm pellet length)	67 ± 8	24 ± 5
<u>Drop test (20 pellets, 2 tests)</u>		
- No of broken pellets (test 1/test 2)	0 / 1	2 / 2
- weight loss (test 1/test 2)	4.4 / 5.0	7.5 / 5.5

Table 4. Drop test results for unused catalysts produced from the same recipes but in different shapes.

Sample	Shape	Fall time (s)	Broken/total	%broken
1	10-mm ring	2.03	12 / 20	60
2	10-mm ring	1.99	21 / 31	68
3	12-mm Daisy	2.15	3 / 20	15
4	12-mm Daisy	2.15	10 / 45	22

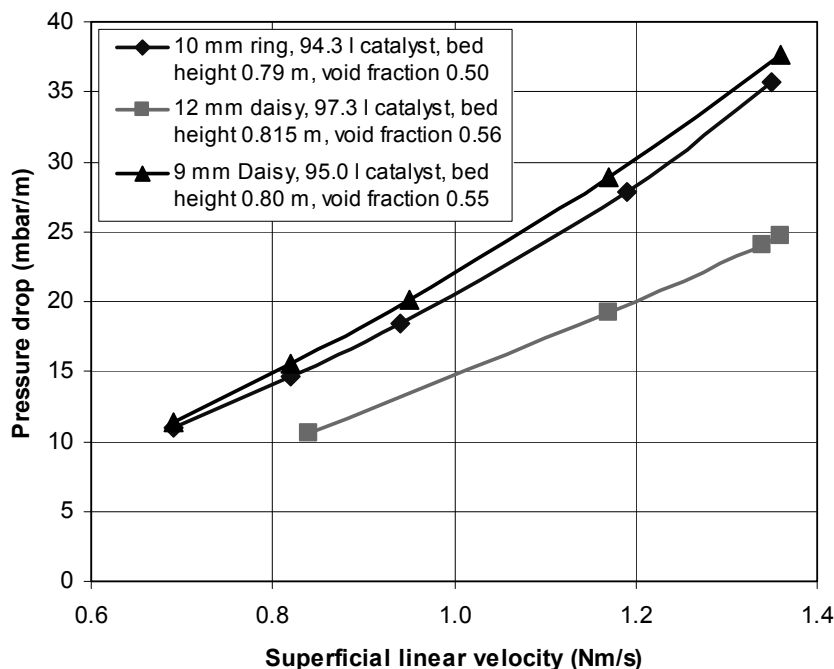


Figure 12. Measured pressure drop for cylindrical rings and Daisy-shapes

11.4.3 Pressure Drop Measurements

The pressure drop for different catalyst shapes (10 mm cylindrical rings, 12 mm Daisy particles and 9 mm Daisy particles) was measured in the set-up shown in Fig. 10 as a function of superficial linear velocity (Fig. 12). The pressure drop per bed height is about 30% lower for a 12 mm Daisy compared to a 10-mm ring primarily due to the lower void of the bed with 10-mm rings (0.50 compared to 0.56). The 9-mm Daisy yields a 5% higher pressure drop than the rings because the higher void is counteracted by the smaller equivalent diameter. It should be noted that the pressure drop of the 12-mm Daisy is only 66% of the 9-mm pressure drop, i.e. lower than the $9/12 = 75\%$ expected from the Ergun equation (5) for equal shapes. The deviation is attributed to the difference in void fraction, which arises from the difference in distribution of particle lengths and in the actual geometry of the pellet ends. This observation illustrates that the theoretical correlations only can be used as a steering tool or an interpolation in the development and that the measured pressure drops are necessary for proper comparison.

The screening of carriers, catalyst composition, particle sizes and shapes showed indeed, that a much more active catalyst could be made with Cs as a secondary promoter for the beds downstream the intermediate absorption tower. The best candidates were selected, and some m³ of each recipe were produced as 9-mm and 12-mm Daisy extrudates in a successful commercial-scale test production. The activities were as expected from the previous development work, and a 30 day activity test also confirmed it to be stable during this period.

11.4.4 Industrial Stability Tests

A canister with several VK69 formulations was also installed in the 4th bed of an industrial 3+1 converter in a 2500 t/day sulphuric acid plant treating off-gas from a copper smelter. After two years of operation at 415°C inlet temperature and 0.7-1% SO₂, the canister was retrieved and the catalysts were analysed as exemplified in Table 5 for one of the candidates with concentrations normalised to the unused catalyst. The results were very satisfactory with unchanged side crush strength and very low deactivation. The small drop observed for the vanadium concentration is primarily due to the 5% weight gain of the catalyst caused by SO₃ uptake according to reaction (2), and the small changes in alkali-metal-to-vanadium ratios were considered to be within the uncertainty of the test. Additional valuable analyses, e.g. elemental composition by ICP and analysis of solid phases by X-ray diffraction, were also carried out but not given in the table. Furthermore, the pore size distribution of the carrier was measured by leaching the melt from the catalyst prior to Hg porosimetry analysis. These analyses provide information on the operating history, potential catalyst poisons, and carrier stability.

Table 5. Results for a VK69 formulation before and after two years of industrial operation.

	Unused catalyst	0-11 cm from top (after 2 years)	23-33 cm from top (after 2 years)
V (relative wt%)	1	0.89	0.97
K/V (relative)	1	0.93	0.93
Na/V (relative)	1	1.02	1.02
Cs/V (relative)	1	1.03	1.04
S/(K+Na+Cs) (molar ratio)	0.77	0.94	0.97
Activity (relative)	1	0.95	0.96
Side crush strength, kp/cm	7	7	8

11.5 Evaluation of Results

The evaluation of carriers and catalyst compositions showed that significantly higher SO₂ oxidation activity could be achieved with Cs as a promoter under the operating conditions downstream the intermediate absorption tower as demonstrated by the results in Table 1, where the activity compared to the standard product is increased by more than a factor 2. This was clearly sufficient for the introduction of VK69 to the market as a new sulphuric acid catalyst. The activity results for different melt compositions were used to optimise the vanadium content and the molar ratios of K/V, Na/V, and Cs/V. However, the choice of Cs/V was not only a question of maximum activity, because of the significant influence of the Cs content on the raw material costs (the price of caesium is 50-100 times the price of potassium on a molar basis). Here, the economic benefits obtained by the sulphuric acid producer by the marginal activity improvement at high Cs content also had to be taken into account.

The laboratory tests as well as the industrial canister tests demonstrated excellent long-term stability of both activity and mechanical strength for the VK69 formulations selected for the tests. For the optimisation of pellet size and shape, the results for activity, fractional void, and pressure drop must be compared as shown in Table 6 for 10 mm rings, 12 mm Daisy-shape, and 9 mm Daisy-shape.

The basis of the comparison is the catalyst bed volume (reactor volume) required to achieve a given SO₂ conversion. The volume is inversely proportional to the bulk activity, which in turn is given by equation (4). For this bed volume, the pressure drop and the net catalyst volume accounting for a fraction of $(1-\varepsilon)$ of the bed volume are compared for the three pellet types. The 12-mm Daisy-shape requires about the same bed volume as the 10-mm ring but the pressure drop can be reduced by 29%. The 9-mm Daisy-shape requires 23% less bed volume than the 10-mm ring giving 19% less pressure drop. The required catalyst volume is important in itself for plants where the SO₂ conversion is limited by the volume of the 4th reactor bed, i.e. the SO₂ emission can only be lowered by installing a more active catalyst and not by adding more catalyst. Above some minimum pressure drop required for even gas flow distribution, a lower pressure drop is always desired but in particular for plants with air blowers operating at their maximum capacity. The significance of the required amount of catalyst material (net pellet volume) is the raw material

consumption - in the case of VK69 especially the more expensive Cs. Because the main market for the new catalyst was expected to be lowering of SO₂ emissions and boosting of production capacity, the more active 9-mm Daisy shape was chosen as the primary product design. For plants with pressure drop limitations, the bed can be loaded with the 12-mm Daisy. The 10-mm ring was ruled out due to the superior activity to pressure drop ratio of the Daisy-shapes.

The comparison in Table 6 illustrates the method but it is only an approximate comparison. In order to account for differences in apparent activation energy between the catalysts, a full reactor model integrating the reaction rate over the full temperature range of the bed is necessary for calculation of the exact catalyst volume.

Table 6. Optimisation of pellet size and shape. The catalyst volume required to obtain a specified SO₂ conversion is the basis for comparison of performance.

Pellet size	10 mm	12 mm	9 mm
Shape	Ring	Daisy	Daisy
Measured pellet activity (relative)	1	1.12	1.45
Measured pressure drop per m bed (relative)	1	0.70	1.05
Measured bed void fraction	0.50	0.56	0.55
Bulk activity (relative)	1	0.99	1.31
Required cat. bed volume (relative)	1	1.01	0.77
Bed pressure drop (relative)	1	0.71	0.81
Net pellet volume (relative)	1	0.89	0.69

11.6 Conclusions

The development of catalysts includes both practical and theoretical knowledge and experience with a palette of disciplines known to the chemical engineer, e.g. inorganic chemistry, physical and chemical characterisation techniques, nano-scale materials, unit operations, chemical reaction engineering, catalyst kinetics, and transport phenomena.

The design of the new sulphuric acid catalyst VK69 by Haldor Topsøe was based on experience from existing products, market knowledge, and an innovative attitude especially in the first stages of development. The

development work did not strictly follow the systematic approach outlined in Fig. 7, because a lot of experience from previous tests and development projects including e.g. identification of critical parameters made it possible to cut corners and bypass steps for some of the VK69 candidates. A systematic and full parametric investigation in each step may strengthen the competencies involved, but from an economic point of view, a more direct route to the goal is preferred because this will reduce the development cost and the time to product launch.

VK69 was introduced in the market by Haldor Topsøe in 1996 and has subsequently been installed in the final passes of more than 50 double absorption sulphuric acid plants worldwide. Due to the superior activity of VK69, the SO₂ emissions can typically be reduced by a factor 2 and new double absorption plants can be designed with less than 40 ppm SO₂ emission [17]. The industrial experience also confirms low deactivation rate and low screening loss as expected from the results obtained in the development phase.

Nomenclature

A_p	Pellet external surface area [m ²]
d_{eq}	Equivalent pellet diameter $=6 \cdot V_p/A_p$ [m]
D_{eff}	Effective diffusion coefficient in the catalyst
k_1	First-order rate constant [Nm ³ gas/h/m ³ catalyst pellet]
Nm ³	Normal m ³ gas at 0°C and 1 atm.
Nm	Nm ³ /m ²
$NHSV$	Normal hourly space velocity [Nm ³ /h/m ³ catalyst bed]
$NHSV_{net}$	Normal hourly space velocity [Nm ³ /h/m ³ catalyst pellet]
P	Total pressure [Pa]
p_i	Partial pressure of component i [Pa]
r_{SO_2}	Rate of SO ₂ production [mole/s/m ³ catalyst pellet]
T	Temperature [°C]
V_p	Pellet volume [m ³]
x	Conversion of SO ₂ [-]
x_{eq}	Equilibrium conversion of SO ₂ [-]
ϵ	Bed void fraction
θ	Thiele modulus
η_b, η_s	Bulk or surface effectiveness factor

References

1. Satterfield, C.N. (1980). *Heterogeneous Catalysis in Practice*. McGraw-Hill Book Company, New York.
2. Villadsen, J. and Livbjerg, H. (1978). *Catal. Rev.-Sci. Eng.*, 17 (2), 203-272.
3. Urbanek, A. and Trela, M. (1980). *Catal. Rev.-Sci. Eng.*, 21 (1), 73-133.
4. Kenney, C.N. (1980). *Catalysis*, 3, 123-135.
5. Lapina, O.B., Bal'zhinimaev, B.S., Boghosian, S., Eriksen, K.M. and Fehrmann, R. (1999). *Catalysis Today*, 51, 469-479.
6. Frazer, J.H. and Kirkpatrick, W.J. (1940). *J. Am. Chem. Soc.*, 62, 1659.
7. Topsøe, H.F.A. and Nielsen, A. (1948). The Action of Vanadium Catalysts in the Sulfur Trioxide Synthesis. *Trans. Dan. Acad. Techn. Sci.* 1, 3-24
8. Mars, P. and Maessen, J.G.H. (1964). *J. Catalysis* 10, 1.
9. Jensen-Holm, H., Livbjerg, H. and Villadsen, J. (1977). In *Chemical Engineering with Per Søltoft*. (ed. K. Østergaard and Aa. Fredenslund), Teknisk Forlag, Copenhagen.
10. Livbjerg, H., Jensen, K.F. and Villadsen, J. (1976). *J. Catalysis*, 45, 216-230.
11. Satterfield, C.N. (1970). *Mass Transfer in Heterogeneous Catalysis*. Massachusetts Institute of Technology, Cambridge, Massachusetts.
12. Bird, R.B, Stewart, W.E. and Lightfoot, E.N. (1960). *Transport Phenomena*. John Wiley & Sons, New York.
13. Fogler, H.S. (1986). *Elements of Chemical Reaction Engineering*. Prentice-Hall, London.
14. Thomas, J.M. and Thomas, W.J. (1997). *Principles and Practice of Heterogeneous Catalysis*. VCH Verlagsgesellschaft mbH, Weinheim.
15. Scott, D.S., Lee, W. and Papa, J. (1974). *Chem. Eng. Sci.*, vol. 29, pp. 2155-2167.
16. Froment, G.F. and Bischoff, K.B. (1979). *Chemical Reactor Analysis and Design*, John Wiley & Sons, New York.
17. Hansen, L. (2004). VK69 catalyst – the proven solution for lower SO₂ emissions, higher production rates. *Sulfuric Acid Today*. Spring/Summer 2004, 22.

Chapter 12

Entrepreneurship and Product Design in Chemical Engineering Education

King Lun Yeung^a

*^aDepartment of Chemical Engineering
the Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong, P.R. China*

12.1 INTRODUCTION

The purpose of this chapter is to share our experience in teaching Chemical Engineering students in Hong Kong the basic elements of successful entrepreneurship and product design through the final year design project. Chemical Engineering is a young profession in Hong Kong with the baccalaureate degree program established in 1993. Despite the lack of traditional chemical industries in Hong Kong, graduates easily find a career in many chemical-related industries and businesses including food and beverage, textiles and clothing, pharmaceuticals and electronics. However, most of these industries emphasize on product rather than process, therefore a good background in product-oriented design is a must. The proximity to inexpensive labor and growing consumer market in China give our students the unprecedented opportunity to establish their own business and enterprise. A basic training in entrepreneurship will be invaluable. Indeed, several alumni had successfully started their own chemical business and manufacturing plant in China.

12.2 BACKGROUND

12.2.1 Geographical, Historical and Cultural Background of Hong Kong

Hong Kong is located east of the Pearl River delta in the province of Guangzhou in southern China. Hong Kong consists of the Hong Kong Island, the Kowloon peninsula, New Territories and the outlying inhabited islands of Lantau and Lamma and hundreds of smaller uninhabited islets. Hong Kong became a British colony in 1842 [1]. Blessed with one of the best natural harbor in the world, Hong Kong became a trading entrepot for Chinese tea, silk and porcelain to England. Today, this legacy made Hong Kong into a vibrant commercial city that adheres closely to the principle of *laissez faire*. 2001 Census showed that ninety five percent of the 6.9 M Hong Kong citizens are of Chinese descent [2]. This gave Hong Kong her distinct eastern tradition and western outlook.

After liberation by the British Army at the end of World War II, Hong Kong had seen influx of immigrants from China, mostly from cities such as Guangdong, Shanghai and Nanking. A great number of the new immigrants were entrepreneurs, banker, financiers, manufacturers and skilled technicians. Their technical know-how, managerial skill and investment savvy transformed Hong Kong in less than a decade into an important manufacturing and trading center in eastern Asia. Textiles, garments, plastics, toys, household appliances and electronics were manufactured and exported. Hong Kong's financial and banking sector also grew with the influx of capitals. The increase in labor and land costs saw the decline of labor-intensive manufacturing in Hong Kong in the late 1970. This and the liberalization of Chinese economy were responsible for the massive relocation of manufacturing facilities to China [1], mostly around the Pearl River delta (Fig. 12.2-1). For the past two decades starting from 1980, the contribution of manufacturing to the overall economy and labor market shrank by eighty percent as shown in Fig. 12.2-2. Today, manufacturing contributes to less than four percent of Hong Kong GDP and employs less than eight percent of the total labor force. Despite the rapid de-industrialization, the overall economy grew by almost forty percent during the ten years period between 1993 and 2002, because of healthy growth in the service sector particularly in the banking, finance, logistic, telecommunication and information technology. This helped alleviate the lost in manufacturing jobs. However the past few years, globalization had eroded Hong Kong's service industry, especially the telecommunication and I.T. sectors. More recently, banking, finance and insurance companies were moving some of their operations to China and India for their cheaper labor. It is imperative for Hong Kong to transform itself into a knowledge-based economy in order not only to survive but also thrive in the decades to come.

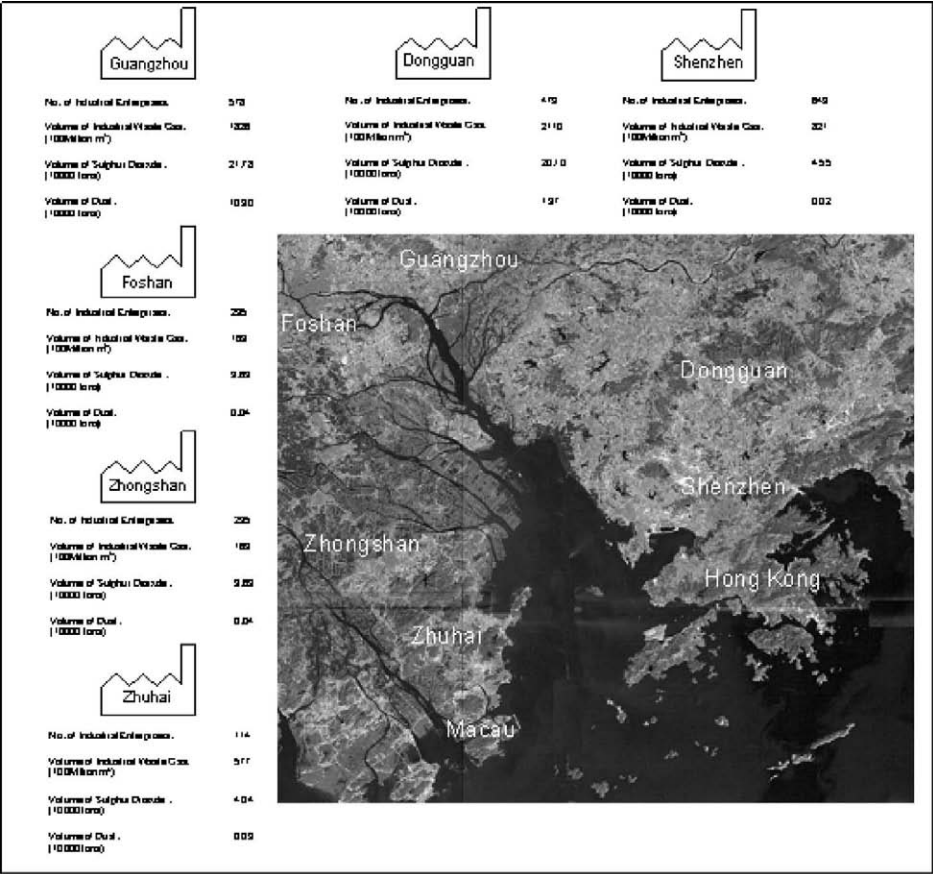


Figure 12.2-1. Industrial development around Pearl River Delta region of Southern China.

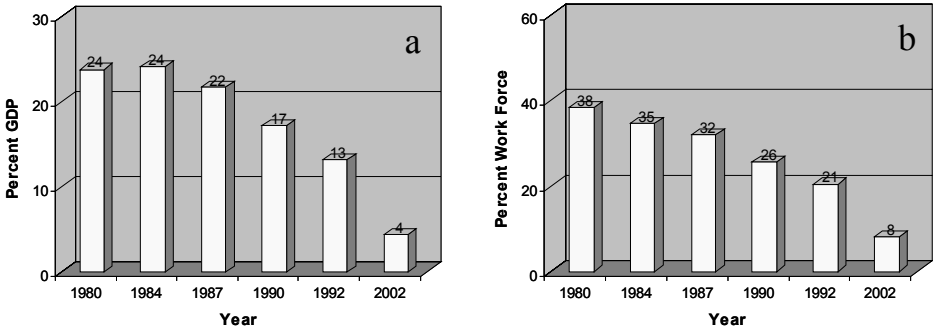


Figure 12.2-2. Manufacturing contribution to (a) overall GDP and (b) total work force in Hong Kong [2]

12.2.2 Chemical Engineering in Hong Kong and Southern China

The chemical engineering profession maintains a small but visible presence in Hong Kong. The Hong Kong Institution of Engineers (HKIE) registered thirty chartered chemical engineers and ninety-three chartered gas engineers. It is estimated that there are about 3000-5000 trained chemical engineers in Hong Kong. The lack of natural resources and high cost of land preclude the construction of large chemical and petrochemical plants in Hong Kong, instead small and medium scale fuel and gas processing plants supplied the local needs. There are more than eleven hundreds chemical and plastic companies and businesses in Hong Kong employing roughly fifteen thousand peoples [3]. Many chemical engineers are employed in local utility companies responsible for Towngas production, electricity generation and water and wastewater treatments. Others contribute to the growth of the local textile and electronic industries that accounts for a third of the employment in manufacturing sector. Chemical engineers are heavily involved in the modernization and mass production of traditional Chinese medicine, food and beverages. Table 12.2-1 summarizes the 2003 data on chemical-related industries and businesses in Hong Kong. An increasing number of chemical engineers are employed in local and multi-national companies with production facilities in China. It is expected that greater demand for chemical engineer will follow upon completion of several major refineries and chemical plants in neighboring Chinese provinces of Guangdong, Guangxi and Fujien.

Table 12.2-1. Chemical-related industries and businesses in Hong Kong [3]

Commodities and Products	Manufacturing		Import and Export Trade	
	Number of Establishments	Workforce	Number of Establishments	Workforce
Alcoholic drinks	22	4011	499	3031
Clothing, footwear and allied products	3063	47850	20537	116381
Consumer goods	1804	8886	31195	148627
Durable goods	494	3309	11985	79926
Foodstuffs	632	24853	3965	17650
Fuel	3	160	202	1897
General commodities	4059	37196	4600	16886
Machinery, equipment and parts	2480	26362	4461	19409
Raw materials and semi-manufactures	3716	25449	18116	81631
Transport Equipment	429	9891	1274	5262
Total	16702	187967	96834	490700

12.2.3 Chemical Engineering Education in Hong Kong

The Hong Kong University of Science and Technology (HKUST) is the only university in Hong Kong that offers a formal Chemical Engineering education. HKUST was conceived by the Hong Kong Governor Sir Edward Youde and Honorable Dr. Sze-Yue Chung to help propel Hong Kong towards a knowledge-based economy by training the next generation of scientists, engineers and entrepreneur how to create and not replicate. The Chemical Engineering department started accepting students in 1993, two years after the University opened its door to students in 1991. The Chemical Engineering undergraduate degree programs are accredited by the Institute of Chemical Engineers (ICHEME) of U.K. and the Hong Kong Institution of Engineers. The latter is a signatory to the Washington Accord and therefore all engineering degrees accredited by the HKIE are recognized by the other signatories. Chemical Engineering education faces unique challenges and opportunities in Hong Kong. The lack of traditional chemical industries and the rapid pace of de-industrialization bring into question the relevance of traditional Chemical Engineering curriculum in Hong Kong. The emphasis of chemical businesses in Hong Kong is on product design and development as well as their manufacture. To be successful, basic business and managerial trainings are a must. New undergraduate course on Products and Processes (CENG 103), as well as language (Lang 001, 002 and 003) and professional development (CENG 001 and 002) courses were introduced. Practical industrial training, computational modeling and simulation, laboratory experimentation and research are important part of the curriculum. Department's participation in the School-level high tech entrepreneur project (HTEP) brought together the important elements of entrepreneurship training, product design and process development in an interdisciplinary environment.

Two undergraduate programs, Chemical and Environmental Engineering (CEEV) and Chemical and Bioproduct Engineering (CBPE), were launched to train students in two emerging industries in Hong Kong. Greater environmental awareness and stricter government regulations motivate manufacturers to develop efficient and green processes and take greater responsibility in environmental management. Besides Chemical Engineering training, CEEV students learn green processes, environmental management, pollution monitoring and abatement. This combined degree enables students to understand various industrial processes and realize where environmental control measures can be implemented, thus making the community a better place to live in. Healthy growth in the local food and beverage industries, increasing demand for new health and personal care products, and advances in life sciences (i.e., pharmaceutical, genetic engineering, bio-MEMs and nanomedicines) are the reasons behind Chemical and Bioproducts Engineering. The program teaches the fundamental principles of chemical engineering along with the new

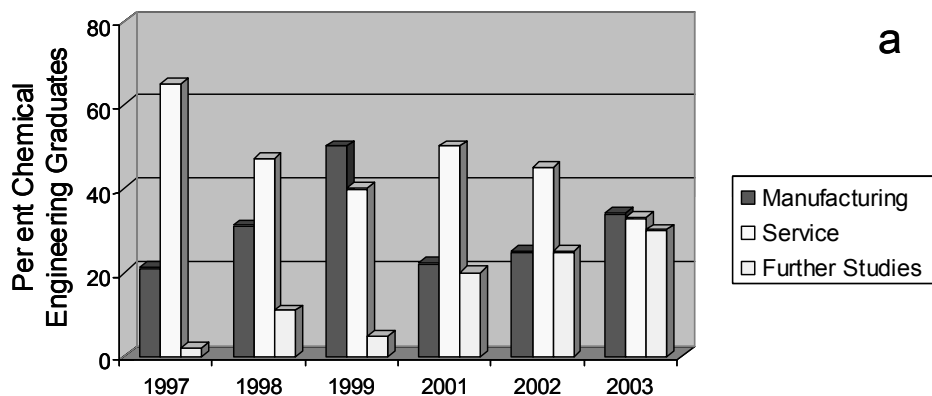
approaches from biology, biochemistry, cell biology and pharmaceutical engineering. Students are trained to use this knowledge for the design and manufacture of bioproducts and biodevices.

Figure 12.2-3 shows that most of the Chemical Engineering graduates found employment in chemical-related manufacturing and service industries. Figure 12.2-3a shows that Hong Kong chemical industries although small compared to other countries are still very much affected by the cyclical trend in worldwide chemical market. In recent years, a growing number of our Chemical Engineering graduates pursued further studies in response to the recent downturn, and growing industry demand for Engineers with Masters or Ph.D. qualifications. Figure 12.2-3b shows the latest distribution of Chemical Engineering graduates according to employment sectors. Over eighty percent of the graduates were employed within six months of finishing their studies.

12.2.4 High Tech Entrepreneurial Program (HTEP)

The six credits, Engineering school-level HTEP courses (ENGG 251 and ENGG 252) were designed by Professors Mitchel M. Tseng and Phil Choong of the Department of Industrial Engineering and Engineering Management (IEEM) at HKUST for final year engineering undergraduate students in lieu of the traditional final year project. The program aims to nurture the entrepreneurial spirits of young engineers and to provide them with an enriching entrepreneurial education. The program allows the students to propose, design and develop engineering products, as well as the opportunity to experience the process of applying for patent, writing business plan and marketing a product. The ultimate goal is to teach the students how to transform an engineering idea into a marketable product. Table 12.2-2 lists the content of the HTEP course lecture.

The program was first launch in Fall 2001 with nine projects and the participation of three engineering departments. Two Chemical Engineering students helped an IEEM-led team in developing a new desiccant formulation for their proposed dehumidifier appliance. Permission was granted by the Department of Chemical Engineering following consultation with IChemE Accreditation Board for substitution of traditional FYP by HTEP for the school year of 2002-2003 with the conditions that key features of chemical engineering design were kept. Table 12.3-1 summarizes the timeline for the HTEP and FYP courses as well as the HTEP research project schedule. The table also shows how the project was designed to satisfy both HTEP and chemical engineering design requirements.



Distribution of Chemical Engineering Graduates by Employment Sector in 2003

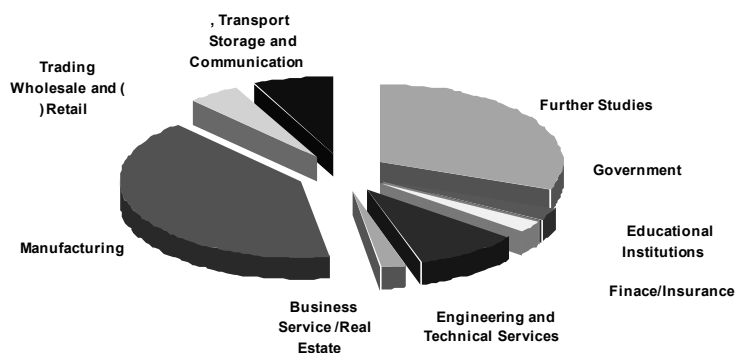


Figure 12.2-3. (a) Percent of Chemical Engineering graduates employed in chemical-related manufacturing and service industries in Hong Kong. The figure also shows the growth in the number of graduates pursuing further educations. (b) Latest data on the distribution of Chemical Engineering graduates by employment sectors.

Table 12.2-2. HTEP course content

-
- Background of Entrepreneurship
 - Value Identification
 - Porter's five forces
 - Competitive Analysis
 - SWOT Analysis
 - Business Model
 - What is your business?
 - Mission and goal
 - How to run the business
 - Revenue mechanism
 - High-Tech Entrepreneurship
 - Role of HKUST R&D Corporation Ltd
 - HKUST Venture Capital Fund
 - Business Plan
 - Outline
 - Executive Summary
 - Business Opportunity
 - Technology Base
 - The Team
 - Strategic Plan
 - Financials
 - Company Law
 - Fundamentals Legal Aspects of a Company
 - Memorandum and Articles of Association
 - Business Niche Discovery
 - Corporate Finance Basics
 - Financials Statements
 - High-Tech Marketing
 - Innovators
 - Early Adopters
 - Early Majority
 - Late Majority
 - Laggards
 - Patents and Intellectual Property
 - Negotiation
 - Identify negotiation
 - Prepare negotiation
 - Negotiation strategies
 - Useful tactics

12.3 PROJECT DESCRIPTION

Poor air quality affects people's health and its human and economic costs are well recognized. People spent more than eighty percent of their time indoor therefore it is imperative to maintain a good indoor air quality. The quality of indoor air is closely related to indoor activities, building construction, ventilation, furnishing materials and quality of outdoor air. Dust, particulates allergens and airborne microorganisms along with gaseous pollutants such as carbon monoxide, formaldehyde and VOCs are common indoor air pollutants. In crowded cities like Hong Kong, ventilation only aggravates the situation by bringing road-side pollutions indoor. This project challenges the student to develop an effective and inexpensive indoor air quality control appliance based on catalyst and adsorbent technologies. The product must be able to remedy

three types of pollutants: (1) dust and particulates, (2) airborne microorganisms and (3) gaseous pollutants (i.e., carbon monoxide and VOCs) associated with odors. These pollutants were selected because of their adverse health impact and their removal can be immediately appreciated by the consumer.

Table 12.3-1. Schedule of 2002-2003 HTEP

Date	HTEP Course ¹	Research HTEP		CENG FYP Course ²	
May – June		Team formation and project selection			
8-Jun	Orientation				
7-Sep	The Age of Entrepreneurship	Market Survey	Literature Review Work Plan Safety Training Order Consumables	Project Description, Evaluation and Costing	
14-Sep	Adaptive Learning and Business Niche Discovery; Raising Capital for Your Own Start-up Company				
28-Sep	Hi-Tech Entrepreneurship: Stimulating a Culture and Helping Start-up Company				
26-Oct	Company Law				
2-Nov	Introduction to Marketing	Business Plan, Business Registration	Computer Simulation: (1) CFD Analysis of air flow and pollutant distribution in indoor; (2) Powder processing; (3) CAD/CAM for product design.	Detailed Process Design and Simulation	
30-Nov	White Paper				
7-Dec	Biotech Evolution and Business Opportunities				
Dec	Submission of Business Plan Draft				
Jan	Winter Break				
5-Feb	Competition and Business Strategy	Product Design: (1) Indoor air survey; (2) Prototype design and construction	Chemical Design and Processing: (1) Adsorbents; (2) Catalysts.	Process Safety Analysis	Report Writing
12, 19-Feb	Library and Presentation Workshop			Process Control and Instrumentation	
26-Feb	Specification of Technology			Environmental Impact Assessment	
5-Mar	Guest Lecture (RF Engineering)				
18-Mar	High Tech Marketing				
8-Apr	Negotiation Workshop				
7-28-May	Intercollegiate Competition	Poster Session and Presentation	Poster Session and Oral Presentation	Poster and Presentation Competitions	
		Presentation to company sponsor			

12.4 HTEP TEAM ORGANIZATION

12.4.1 Team Organization and Resource

Eight final year undergraduate students from both Chemical Engineering and Chemical and Environmental Engineering programs (Table 12.4-1) were recruited for the project. Students were asked to form four teams, one for each major task identified for the project. Each team was assigned a postgraduate student mentor to oversee the day-to-day operation. A student project leader was elected every two months to take responsibility of coordinating the team, conducting progress assessment, overseeing the project's budget expenditure and scheduling regular meetings and reports. One undergraduate student from the School of Business was recruited to help in the market survey and business plan writing. Other undergraduate students joined towards the end of the project to help the team in prototype testing.

Table 12.4-1. HTEP team members

Team Member	Degree Program
Indoor Air Survey Team (PG Supervisor: Ms. Prudence LAU Pui Sze)	
Ms. Phoebe LUI Pik Ying	B. Eng. Chemical and Environmental Engineering
Mr. Lawrence WONG Wah Tak	B. Eng. Chemical and Environmental Engineering
Catalysts Team (PG Supervisor: Ms. Alice HO Ka Yee)	
Mr. Cyber HUNG Tak Cheong	B. Eng. Chemical and Environmental Engineering
Mr. Michael KWAN Siu Ming	B. Eng. Chemical and Environmental Engineering
Adsorbent Team (PG Supervisor: Ms. Prudence LAU Pui Sze)	
Mr. Tsz Chun NG	B. Eng. Chemical Engineering
Mr. Clark SUN Wenqing	B. Eng. Chemical Engineering
Prototype Design Team (Industry Advisor: Mr. Anthony NG Ka Hang)	
Mr. Raymond LO Siu Kee	B. Eng. Chemical and Environmental Engineering
Mr. Chi Chi NGAN	B. Eng. Chemical and Environmental Engineering
Business Team	
Mr. Bobby POON Chi Hung	B.B.A. Finance

A panel of experts from academia and industry (Table 12.4-2) was assembled to provide the students with professional advice. The HKUST central facilities for Material Characterization and Preparation Facility (MCPF) and Advanced Engineering Material Facility (AEMF) and the laboratories of Department of Chemical Engineering, Department of Industrial Engineering and Engineering Management, Department of Mechanical Engineering and Advanced Technology Center play a pivotal role in the success of the project. Table 12.4-3 lists the equipment used by the students in this project.

The students find the following Chemical Engineering undergraduate courses listed in Table 12.4-4 relevant to the project. The students audited several courses including the post-graduate courses, Theory and Practice in Heterogeneous Catalysis (CENG 511) and Measurements of Air Pollutants (CENG 531). The prototype design team attended the CAD/CAM course (MECH 251) of the Mechanical Engineering Department.

Table 12.4-2. Team of experts

Name/Affiliation	Expert Advice
Prof. Ming FANG Institute for Environment and Sustainable Development, HKUST	Pollution measurements and abatements
Prof. David C. W. Hui Chemical Engineering, HKUST	Pinch analysis, system optimization
Dr. Arthur P. S. LAU Applied Technology Center, HKUST	Bioaerosol measurements
Mr. Victor LO Vice President, Honeywell Hong Kong	Home appliance market
Mr. Anthony NG Ka Hang Engineer, Honeywell Hong Kong	Prototype design and construction
Mr. King Lun TO Applied Technology Center, HKUST	Air sampling and VOC measurements
Prof. Mitchell M. Tseng Industrial Engineering and Engineering Management, HKUST	Mass customization, product design and manufacture
Mr. Eddy WU General Manager, Chiaphua Industries Ltd.	Appliance design, costing and manufacture

Table 12.4-3. Research facilities and equipment

Facility	Analysis	Access	Cost
Advanced Engineering Materials Facility (AEMF)			
Nitrogen physisorption <i>Coulter SA 3100</i>	BET surface area and pore size distribution	Trained	Free
Ovens and furnaces	Adsorbent and catalyst calcination	Trained	Free
Zeta potential meter	Surface Zeta potential and particle size distribution	Trained	Free
Advanced Technology Center (ATC)			
Aerosol sampler <i>Dust-Trak Air Monitoring (Model 8520)</i>	Airborne particulate size and counts	Trained	Free
Bioaerosol sampler <i>SKC BioStage® Bioaerosol Impactor</i>	Airborne bioaerosol counts	Trained	Free
Thermocouple and hygrometer <i>Cole-Palmer Thermohydrometer (DW-37950-10)</i>	Ambient temperature and humidity	Trained	Free
Incubation oven	Bacteria and Fungi incubation	Trained	Free
VOC analysis <i>Sorbent tube, Tubsomatrix Thermal Desorber and HP 6890 Gas Chromatograph</i>	Formaldehyde, BTX (benzene, toluene and xylene)	Trained	Free
Sterilizer	Sterilization of culture plates and glasswares	Trained	Free
Department of Chemical Engineering			
Process simulation <i>ASPEN</i>	Nanomaterial processing	Trained	Free
Atomic force microscopy (AFM) <i>Digital Instrument Nanoscope IIIa</i>	Nanoparticle size and morphology	Trained	Free
Gas analyzer (CO & CO ₂) <i>PCO2 Plus Versatile dual gas analyzer</i>	Ambient carbon monoxide and carbon dioxide level	Trained	Free
Computational fluid dynamic simulator <i>FEMLAB</i>	CFD simulation of indoor air flow and pollutant dispersion	Trained	\$

Table 12.4-3. Research facilities and equipment – *cont.-1*

Facility	Analysis	Access	Cost
Department of Chemical Engineering (cont.)			
Fourier transformed infrared spectroscopy (FTIR) <i>Perkin-Elmer GX 2000</i>	Surface chemistry, adsorbed species, reaction mechanism	Trained	Free
Gas Analyzer <i>Photoacoustic Machine (Model 1302)</i>	Formaldehyde, carbon monoxide, carbon dioxide	Trained	Free
Gas chromatography (GC) <i>Howitt-Packard 6890</i>	On-line reaction study, off-line sample analysis	Trained	Free
Inductively coupled plasma, atomic emission spectrometer <i>Perkin-Elmer Optima 3000XL</i>	Catalyst loading and bulk composition	PG	\$
Oven (convection, microwave, vacuum)	Adsorbent and catalyst preparation	Trained	Free
Syringe pump <i>KdScientific 1000</i>	VOC metering and feed	Trained	Free
Temperature programmed desorption/reduction/oxidation <i>Altamira</i>	Active site identification and analysis	PG	Free
UV-visible spectroscopy	Concentration measurements	Trained	Free
Design & Manufacturing Services Facility			
CAD/CAM Software <i>SolidWorks</i>	Prototype design	Trained	Free
Control box	Temperature controller and programmable units	Technician	\$
Sensors and sensor box	Circuit design and construction of sensor box	Technician	\$
Engineering School			
Aerosol impactor <i>Dust-Trak Air Monitoring (Model 8520)</i>	Airborne particulate size and counts	Trained	Free
Air pump	Air sampling	Trained	Free
Glassblowing Facility			
Glasswares <i>Reactors, adsorption glasswares</i>	Glassware design and fabrication	Technician	\$

Table 12.4-3. Research facilities and equipment – *cont.-2*

Facility	Analysis	Access	Cost
Department of Industrial Engineering and Engineering Management			
Rapid Prototyping	Preparation of a 1:4 prototype of external casing	Technician	\$
Department of Mechanical Engineering			
Air flow meter <i>VelociCalc Plus (Model 8306-M-G8)</i>	Prototype air flow measurement	Trained	Free
Sound measurement <i>Rion Interacting Sound Level Meter (NL04)</i>	Noise level	Trained	Free
Material Characterization and Preparation Facility (MCPF)			
Electron microscopy (TEM, SEM)	Particle size distribution, particle shape and morphology	PG	Free
Micro-Raman spectroscopy	Crystal phase structure, crystal size, surface metal oxide structure and coverage	Trained	Free
Thermogravimetric and differential thermal analyses <i>Selaram 31/1190</i>	Phase transition temperature	Trained	Free
X-ray diffraction (XRD)	Crystal phase structure and crystal size	Technician	Free
X-ray photoelectron spectroscopy (XPS) <i>Physical Electronics PHI 5000</i>	Surface composition and oxidation states	Technician	Free

Table 12.4-4. Chemical Engineering relevant to the project

CENG 099 Industrial Training For students of the Chemical Engineering Department only. A practical training course for a total duration of about eight weeks covering electro-plating, photo-chemical etching, metal surface finishing, plastic technology practices, CAD, drawing, process instrumentation, process simulation, air pollutant measurement, and safety.
CENG 151 Introduction to Materials Science and Selection Materials fundamentals: atomic bonding, crystalline structure, imperfection, phase diagrams and kinetics. Materials: metals, ceramics, plastics and composites. Materials selection for the chemical process industries.
CENG 152 Introduction to Environmental Engineering Fundamentals of environmental engineering. Sources of pollution. Pollution problems in water, air, on land and from noise and waste energy. Global pollution. Overview of pollution prevention and minimization.
CENG 211 Reaction and Reactor Engineering Stoichiometry and reaction equilibria. Homogeneous reactions kinetics. Mole balances: batch, continuous-stirred tank and plug flow reactors. Collection and analysis of rate data. Catalytic reaction kinetics and isothermal catalytic reactor design. Diffusion effects.
CENG 377 Introduction to Air Pollution Control Introduction to absorption and adsorption, scrubbing, stripping, membrane separation, incineration, catalytic reduction, particulate removal using settling chambers, cyclones, electrostatic precipitators, filters, and wet collectors.
CENG 398 Investigation Project Students conduct in-depth experimental/computational investigations on selected topics in one of the departmental research areas. Students work under supervision and are encouraged to use their own initiative to complete an appropriate program of work within the

12.4.2 Management Tools 101

The students were taught a number of management tools essential for the efficient operation of the project [4]. These include:

12.4.2.1 Time Management

Time management is essential for the students, who had to balance their time commitment to the project and the workloads from the other courses. They were also required to take an additional six credits course in the school level, high tech entrepreneurship program (HTEP) for both Fall and Spring semesters. Each semester, the students were asked to monitor their activities for one week period, rank the activities in term of priority and calculate the amount of time used. The students were then asked to reassess their time usage and create an action plan.

12.4.2.2 Critical Path Analysis

Critical path analysis was used to identify the major tasks needed for the successful completion of the project. The team met to make the worst and best case projection for the project completion. Project tasks and subtasks were listed on separate index cards. The cards were arranged on a bulletin board in sequential orders and colored pens were used to mark the connectivity and flow of the various tasks. Different task arrangements were explored taking into account the project objectives, student training and the available time and resource for the project. The best arrangement was to subdivide the team along four semi-independent tasks. These are the indoor air quality survey needed to obtain a better understanding of indoor air pollution in Hong Kong households; design of a high capacity, regenerable VOCs adsorbent; formulation of an

efficient, low temperature oxidation catalysts to convert airborne VOCs into harmless carbon dioxide and water; and construction of a working prototype for indoor air quality control appliance based on the new adsorbent and catalyst materials.

12.4.2.3 Skill Matrix and Team Working

Skill matrix was used to assess the skills and weaknesses of the team members and help select the best team composition for each of the four major tasks identified by the critical path analysis. The process involved the whole team and started with the listing of the essential background and skills needed for each task. After grouping together related skills, the ten most important skills were selected. Individual team member then rate themselves in the scale of 1 (poor) – 5 (excellent) against each skill. The result was analyzed and discussed in a friendly and informal environment to promote honest self-assessment. Each member was also asked to rank each topic in order of preference and list three individuals that they would like be partnered with. The final team composition was decided based on the skill matrix and individual preferences. The team working principle was used to enable the team to work more effectively together. The discussion was done to identify issues, gaps and areas for improvement within the team. The purpose is to create a good working environment and encourage teamwork.

The students used the Gantt chart to plan and monitor the project progress. Each team prepared a detailed list of tasks, milestones and deliverables. A timeline was constructed based on the completion time, delivery schedule and estimated time needed to complete each tasks. The Gantt chart enabled the students to identify dependency between various tasks and recognize potential bottlenecks in the project. The critical tasks, scheduled tasks, completion dates and delivery time were clearly labeled. Each week the teams met to discuss and update the Gantt chart, as old tasks were completed and new one started.

12.4.2.4 Decision Mapping, Decision Table and Effort Impact Graph

Experienced engineers and professionals can often intuitively make the correct decision given a number of options [5], however this cannot be expected of young students. The students were taught how to use decision mapping, decision table and effort impact graph to guide their decision process. A high-level process diagram for decision mapping is illustrated in Fig. 12.4-1 [4]. The diagram clearly defined each steps of the decision process and their relationship to one another. The quality, confidence, time and cost of the decision are taken into account during the process. Decision table was then employed to select the best alternative from a number of options. This involves listing the judging criteria and their relative importance (i.e., weighing factor). Using a score of 1 (poor) – 5 (excellent), the various options were scored against the listed criteria and the overall score was used to guide the decision. It is important to note that

this decision is still far from being objective since the weightings and criteria scores are often based on subjective opinions. The effort impact chart was used to visualize the relative effort needed for each alternative options and its overall impact on the project.

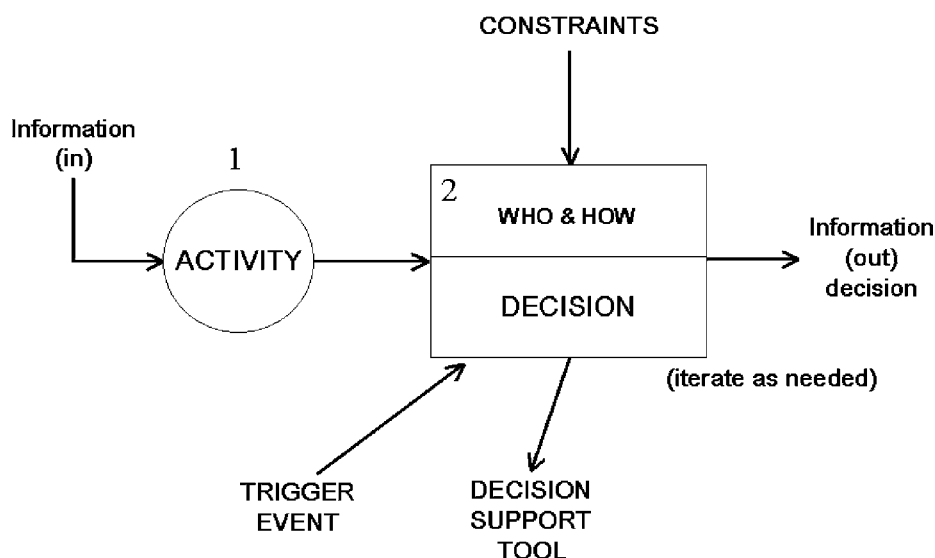


Figure 12.4-1. An illustration of the decision map.

12.4.2.5 Brainstorming

Regular brainstorming sessions were conducted during the duration of the project involving the whole team and invited guests. Creative solutions and designs were established during these sessions. Each session dealt only with one design or process problem. Ideas are encouraged by allowing each team to pre-work the problem beforehand. The sessions were informal and freewheeling, with all ideas being welcomed. The assessment was conducted in a friendly and constructive way. Principles of pre-work and forced combination were employed to provide better structure to the brainstorming sessions.

12.5 BUSINESS PLAN

The students were asked to draft a business plan early in the project to better understand the product requirements. It served as an important guide in the product design and development. This section discusses only the main elements of the business plan.

12.5.1 Product Description and Production Strategy

The product is a household appliance designed to deliver clean air by removing and killing airborne microorganisms, and converting carbon monoxide and common VOCs found indoor into harmless carbon dioxide and water. It also dehumidifies indoor air and maintains a comfortable humidity level that suppresses fungal proliferation. The appliance is intended to maintain its performance without maintenance for at least two years and is expected to have a functional life of at least five years. The product contains an active formulation of (1) low temperature oxidation catalyst, (2) VOCs adsorbent and (c) desiccant.

An efficient, low temperature oxidation catalyst was developed based on highly disperse metal catalyst on nanostructured TiO_2 support. Addition of dopants inhibits metal sintering and prevents catalyst deactivation. The nanostructured catalyst was formulated to tolerate common poisons found in environments such as halogen- and sulfur-containing compounds. The nanocatalyst is capable of oxidizing carbon monoxide and common VOCs to carbon dioxide and water at near ambient temperatures (25-50 °C).

Chemical and structural modification of mesoporous silica produces a regenerable adsorbent with large adsorption capacity for VOCs, fast adsorption rate, excellent regenerability (i.e., lower regeneration temperature and faster regeneration) and superior hydrothermal stability than the original MCM-41. A new desiccant formulation was prepared from a mixture of submicron-sized silica gel and molecular sieves to achieve the best combination of large water capacity, rapid water adsorption and easy regenerability. The formulation also tolerates the presence of VOCs and smokes.

The team agreed that the production of (1) low temperature oxidation catalyst, (2) VOCs adsorbent and (3) desiccant should be the core business of the new enterprise and the appliance manufacture should be conducted through strategic partnerships with Chinese OEMs. The enterprise will produce the catalyst, adsorbent and desiccant in suspension, paste and powder forms as needed for their incorporation in the appliance. Honeycomb filter made of the formulated powders will also be one of the main products. The enterprise will design the appliance and provide the blueprint along with components containing the active formulation to the OEM partners. The OEM manufacturers will be responsible for the manufacture of mechanical and electrical components and their assembly into an appliance.

12.5.2 Market Analysis

The project team with the help of Mr. Eddy Wu of Chiaphua Industries Ltd. and Mr. Bobby Poon Chi Hung, an undergraduate business student, conducted a detailed market survey and analysis.

12.5.2.1 Market needs

Hong Kong is densely populated with only about 100 square kilometers of land available for residences, commerce and industries [6]. The lack of local heavy industries means that vehicular emission is the major source of city's air pollution. Hong Kong has roughly 400,000 private vehicles and despite the government's best efforts to reduce the pollution emission by banning the sales of leaded petrol starting April 1999 and by tightening the regulation on sulfur content of diesel fuel to 0.005 % starting from April 2002, the local Air Pollution Index (API) remained "high" for more than 300 days of the year. Notwithstanding the introduction of liquefied petroleum gas (LPG) taxi scheme by the Environment, Transport and Works Bureau in 1999 to further decrease the carbon monoxide, hydrocarbons, NO_x and particulate emissions from city taxis, the number of days with "very high" API has been increasing for the past few years [7]. The proximity of Hong Kong to the heavily industrialized Pearl River Delta may be a contributing factor to the city's worsening air pollution. Indeed, a recent study [8] shows that pollution in summer is lower when the prevailing wind comes from the South China Sea, but considerably worsened during the winter months when the wind blows from the north bringing in the pollutions from the Pearl River Delta.

Hong Kong's population of more than seven millions people lives in less than 70 square kilometers of land [6] with most of the two million households concentrated within the two narrow strips of lands in Kowloon peninsula and Hong Kong Island that border the Victoria Harbor. A typical Hong Kong household has an average of 3.2 family members and lives in a high-rise apartment of an average size of 40 m². A medium-sized, HK apartment building houses around 200 families and poor indoor air quality is a growing concern of the residents. Many reports [9] showed that indoor air quality could be ten times worse than outdoor because of poor air ventilation. This can be vividly experienced by simply strolling down an apartment corridor, where one is assaulted with a riot of odors from cooking, incenses, smokes, deodorizers and disinfectants. Hong Kong has a humid weather with average relative humidity of about 80 % throughout the year [10]. Summer is hot and humid with a monthly rainfall of more than 300 mm. The humidity encourages the growth of fungi and mildews, those spores can triggers allergic reaction and even asthma.

Poor indoor air quality is believed to be responsible for the high number of asthmatic children in HK (10.1 %) compared to neighboring cities in the region,

and this number has been increasing over the years from 4.8 % in 1989 to 11.2 % in 1995 and 17.2 % in 2002 [11]. Other children respiratory illnesses such as rhinitis (42.4 %), nasal allergy (37.4 %) and wheezing (9.4 %) are also showing a rising trend [12]. Besides children, Hong Kong's ageing population is also at a greater risk from respiratory diseases. Hong Kong is not a stranger to disease outbreaks. There was the bubonic plague in late 1800, the Hong Kong flu (H3N2) in 1968, the avian flu (H5N1) in 1997 and the Severe Acute Respiratory Syndrome (SARS) that occurred early March 2003 during the later part of this project. Government report suggested that poor building ventilation design played a role in the spread of SARS virus at Amoy Garden Apartment Block E where about 213 residents were infected. It was believed that aerosolized fecal matters from an infected resident were spread by ventilation to neighboring flats.

An air-cleaning appliance capable of trapping, killing and eventually mineralizing airborne microorganisms, as well as removing and converting harmful carbon monoxide, volatile organic compounds (VOCs) and odors into harmless carbon dioxide and water to deliver clean air, is therefore highly desirable.

12.5.2.2 Market Survey

Hong Kong economy was in recession from 1999 until 2003 following the Southeast Asian economic crisis. The economy suffered further downturn during and after the SARS outbreak of 2003 resulting in record high unemployment and a deflationary market, which mean lower consumer purchasing power. Unlike Japan where air cleaner is considered a common household appliance, less than 1 % of surveyed Hong Kong households owned an air cleaner. However, 93.3 % of Hong Kong families have at least one air conditioner and 56.7 % have dehumidifiers. It is therefore attractive if the technology can be implemented using either air conditioner or dehumidifier as an appliance platform. A 2-in-1 appliance would appeal to the price-conscious consumers and enables the new technology to rapidly penetrate the market. A decision was made to use the dehumidifier as a platform for the new technology.

The market survey also revealed that when buying an air cleaner, 23 % of Hong Kong consumers place high priority on the price; 19 % decide based on the appliance's ability to remove harmful particulates and 15 % consider the ability to eliminate odor important. In purchasing a dehumidifier, the decision was made mainly based on the price (25 %) and capacity (22 %). Eighteen percent of the people surveyed would consider air-cleaning function an attractive feature for the dehumidifier. The targeted market segments are households with mid-to-high level incomes, who are best able to afford and are more willing to pay for the added air-cleaning function in their dehumidifier. The survey data in

Fig. 12.5-1 shows that Hong Kong population is ageing and becoming better educated. The middle-aged and better-educated city residents are more health conscious and should be more willing to adapt new innovative products.

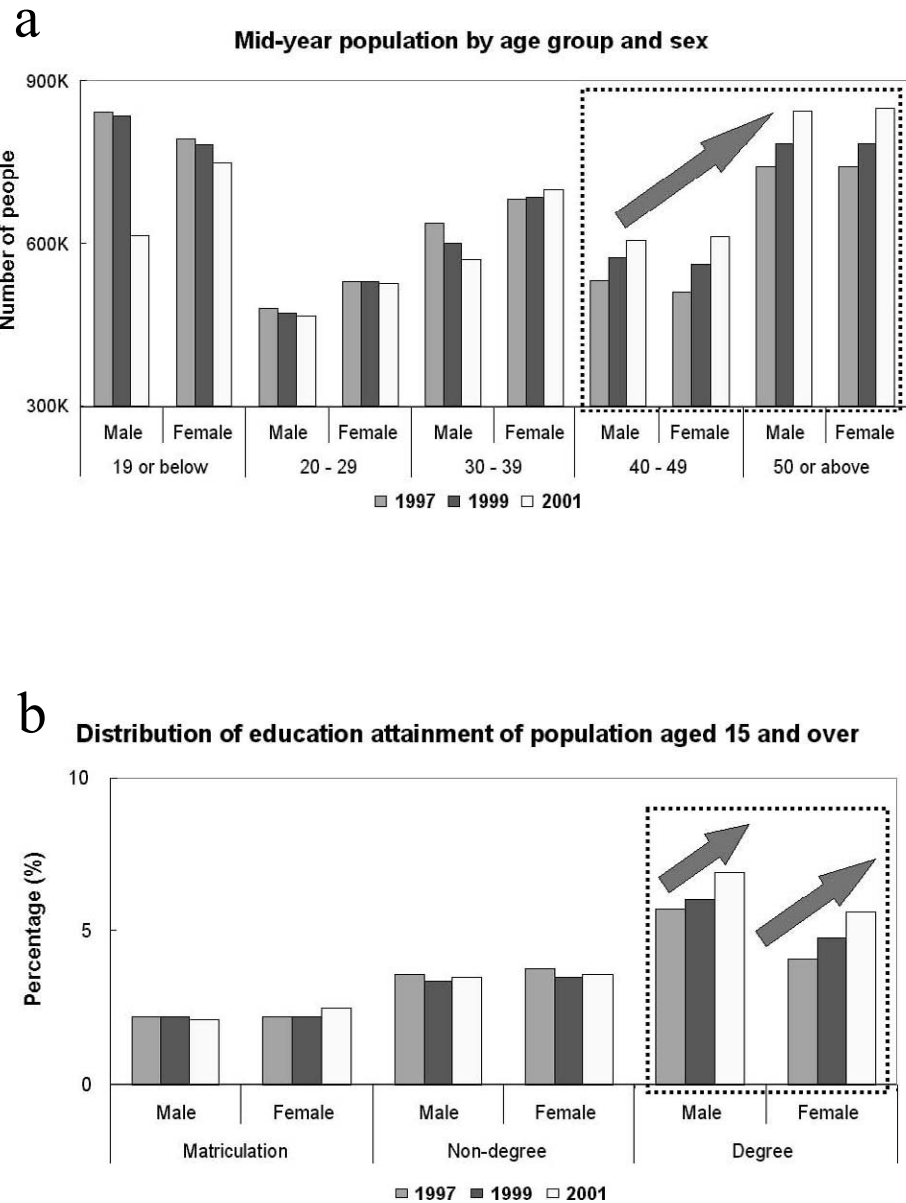


Figure 12.5-1. Market survey of Hong Kong consumer population in term of (a) age and (b) education.

12.5.2.3 SWOT and VIRO Analyses

The SWOT and VIRO analyses shown in Tables 12.5-1 & 12.5-2 were conducted to better understand the strengths and weaknesses of the product and available resources needed for the success of the enterprise. SWOT analysis of competitors was also carried out to identify areas where the product can gain competitive advantage.

Table 12.5-1. SWOT analysis of the product.

Strengths: <ol style="list-style-type: none"> 1. Effective against the complete range of indoor air pollutants including organic- & bio-aerosols, VOCs, odors and carbon monoxide; 2. New advanced technology; 3. Inexpensive material; 4. Easy to manufacture. 	Weaknesses: <ol style="list-style-type: none"> 1. Unable to remedy inorganic aerosols; 2. Low clean air delivery rate (< 100 cfm); 3. Produces carbon dioxide.
Opportunities: <ol style="list-style-type: none"> 1. Large potential market and growth prospects; 2. No product of similar performance available in the market. 	Threats: <ol style="list-style-type: none"> 1. Market acceptance of new technology; 2. Confusion between new and old technologies.

Table 12.5-2. VIRO analysis of the enterprise.

Valuable: <ol style="list-style-type: none"> 1. Catalyst and adsorbent could be easily manufactured; 2. The proprietary composition is difficult to imitate. 	Rare: <ol style="list-style-type: none"> 1. Catalyst is relatively new technology for indoor air cleaners; 2. Regenerable adsorbent is new for the industry.
Inimitable: <ol style="list-style-type: none"> 1. Protected by patents; 2. Customisation for different market segment is accomplished by using different product formulations. 	Organization (ORG): <ol style="list-style-type: none"> 1. Investment money is needed to setup a company; 2. Profit sharing with strategic partners.

12.5.3 Competitor Analysis

The majority of air cleaners are designed to remove dust and allergens from the air. The mechanical air cleaners use filters to trap and remove the particles from air drawn in by the appliance. They often employ medium- to high-efficiency filters that have rated efficiency between 20-60 %. The filters are either disposable or reusable (i.e., washable filters). The high-efficiency filters are often mistakenly marketed as HEPA-type filter. The characteristics of true HEPA filter are summarized in Table 10. Air cleaners that employ electrostatic precipitators and ionizers to remove airborne particles are categorized as electronic air cleaners. Electrostatic precipitators use a small electrical charge to collect particles from air pulled through the device, while ionizers produce negative ions that causes airborne particles to stick to materials around the vicinity of the appliance. Table 12.5-3 lists their respective strengths and weaknesses.

Table 12.5-3. Competitor analysis – *cont. 1*

Advantages	Disadvantages
HTEP Filter	
99.97% removal efficiency for 0.3 microns particles;	Very high pressure drop;
Particle removal efficiency increases with use;	Large fans is noisier and consumes more energy;
Long maintenance-free life of up to one year, five years when used with prefilters.	Replacement filter costs between US\$50 to US\$100.
Electrostatic Precipitator	
Established technology for removing dust, condensable organics (e.g., oil) and cigarette smoke;	Removes at best 40-50 % of larger particles ($> 0.3 \mu\text{m}$);
No filter to replace.	Requires constant maintenance;
	Low clean air delivery rate.
Ionizer	
Established technology for removing dust;	Ions distribution is uncertain and unpredictable;
Compact design	Generates secondary pollution in form of dusts deposited around the vicinity of the appliance;
No filter to replace.	Ineffective against gaseous pollutants;
	Requires constant maintenance.

Table 12.5-3. Competitor analysis – cont. 2

Advantages	Disadvantages
Adsorbents (Activated carbons and charcoals)	
Large adsorption capacity for VOCs and odors;	Inefficient for removing low molecular weight pollutants such as formaldehyde and ammonia;
Immediately noticeable effects;	Adsorption decreases rapidly with time and frequent replacement is required.
Operates well even under very humid conditions.	
Ultraviolet Irradiation and Photocatalytic Oxidation (PCO)	
Established method for inactivating biological agents;	High power consumption;
Kills bacteria, protozoa, molds, fungi, yeasts, spores and viruses;	Possible generation of secondary pollutants including ozone and PCO byproducts;
PCO converts organic pollutants into carbon dioxide and water.	Expensive and complicated appliance design;
	Require expensive lamp replacement.
Ozone	
Induce particle precipitation as in the case of ionizers;	Ozone is a harmful pollutant and banned in most countries;
Efficient odor removal.	Requires periodic cleaning and maintenance;
	Causes rapid ageing and discoloration of room furnishings.

Odors associated with gaseous pollutants are often treated by adsorption on activated carbons and charcoals. Permanganate-coated alumina is known to be also effective in removing persistent odors. Photocatalytic oxidation (PCO) using UV-irradiated TiO_2 catalyst is popular in Japan for treating organic air pollutants and is proven effective for smokes and odors. UV-irradiation is also known to inactivate a wide-range of bacteria, fungi, spores and viruses. Ozone air treatment devices are still popular in Asia despite the established health risks associated with this technology. A comparison of the various technologies is shown in Table 12.5-3.

It is not unusual for air cleaners to employ two or more of the technologies listed in Table 12.5-3 to achieve the desired target performance and cost. This is particularly true for most air cleaners in Asia where the design includes coarse prefilters, high-efficiency filter package, activated carbon, ionizers and often one or more unconventional technologies such as germicidal filter, PCO and air freshener. The latter is used mainly as marketing ploy. The price range of these products is from US\$100 to US\$ 400 depending on the technology and design.

12.5.4 Generic Competitive Strategy

The students identified the best competitive strategy for the product and company is to focus on a single market segment (Fig. 12.5-2) and avoid direct

competition with established companies that could easily afford better price and provide a larger range of products. Both product and technology being new require a different marketing approach since different people have different adoption rates with some liking new things, while others only purchase tried and tested products.

The innovators prefer buying things that are new and will be targeted through magazine advertisements and home shopping network. Product test by this group will be conducted prior to mass production in order to fine-tune the design. The students also proposed to market the product to new residential and commercial buildings with environmental design concepts through partnerships with real state developers and apartment renovators to create a group of early adopters. To reach the peoples belonging to early and late majorities, product tests and certifications by established laboratories and consumer organizations would be sought. Testimonial and print advertisement will be launched. Discounted price, rebates and refunds will be considered to attract more costumers. Partnership with retail industries will be important to reach larger costumer base.

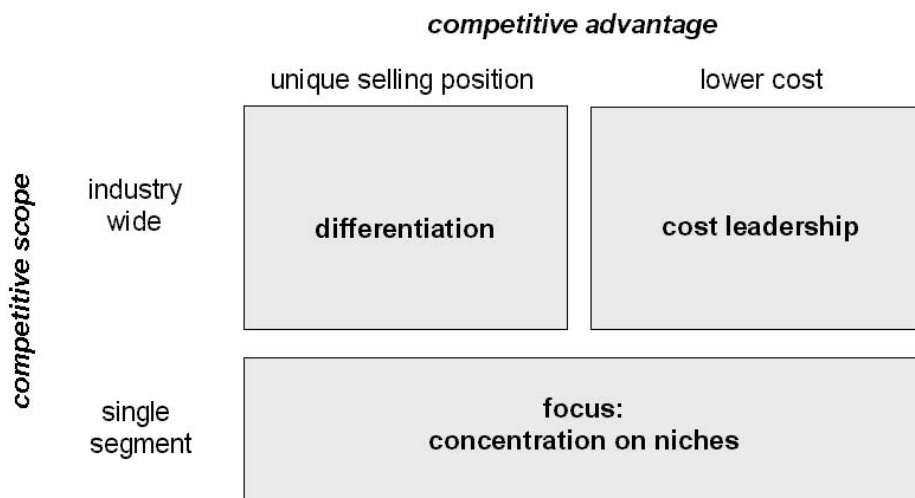


Figure 12.5-2. Identifying the generic competitive strategy.

12.5.5 Company Formation

The project team drafted and signed a “Memorandum of Association” and “Article of Association” shown in Fig. 12.5-3 & 12.5-4 establishing a “virtual” company named Gryphon Technologies Limited. The purpose of this exercise is to teach the student the basic steps and legal aspect of forming a company.

<p>Memorandum of Association</p> <p>Gryphon Tech. Limited</p> <p>1. The name of the company is "Gryphon Tech. Limited".</p> <p>2. The registered office of the company will be situated in Hong Kong.</p> <p>3. The objects for which the company is established are conducting all the business activities related to air quality control technology. In the case of an association referred to in section 2(11) or a company referred to in section 2(12), the objects should be set out here in any other case if the objects are being stated they should be set out here (formulated in 1997, p. 56)</p> <p>4. The liability of the members is limited.</p> <p>5. The authorized share capital of the company is HKD \$10,000, subject to increase by passing an ordinary resolution. It consists of 10,000 ordinary shares HKD \$0.11 per value per share and equally shared by nine shareholders. The company can at any time increase the amount of authorized share capital and number of shares by passing an ordinary resolution provided that such increase is permitted by the company's Article of Association.</p> <p>WY, the several persons whose names, addresses, and descriptions are hereinafter specified, are desirous of being formed into a Company in pursuance of this Memorandum of Association.</p> <p>Names, Addresses and Descriptions of Subscribers</p> <p>NGAN Chi Chi CEO / Chief Executive Officer</p> <p>WONG Kiu Yee Chun Accounting & Finance</p> <p>Michael KWAN Siu Ming Research & Development</p> <p>Lawrence WONG Wei Tin Human Resources & Administration</p> <p>Robby POON Chi Hung Marketing & Key account Management</p> <p>Phoebe LUI Ng Ying Marketing & Key account Management</p> <p>Cyber HU Nai Tak Cheung Supply Chain Management</p> <p>Chin SUN Wai-ping Research & Development</p> <p>Raymond LO Siu Kiu Accounting and Finance</p> <p>Dated 23 November 2002</p> <p>Witness to the above signatures,</p> <p>Raymond Y. C. Tang, Arthur K. H. Chan & Co. 150 Floor, United Centre, No. 95 Queenway, Hong Kong, Solicitor & Notaries</p>	
---	--

Figure 12.5-3. A copy the students’ Memorandum of Association.

<p>Articles of Association</p> <p>Gryphon Tech. Limited</p> <p>1) Administrative bodies of the company</p> <p>The company's administrative bodies are the Board of Directors and the President & CEO. The company can furthermore have one or more Deputy CEO.</p> <p>2) Board of Directors</p> <p>It is the duty of the Board of Directors to manage the company's operations in accordance with the regulations of this law and the Articles of Association. The Board of Directors is composed of a Chairman, Vice Chairman, and five or less than six non-executive members.</p> <p>The Chairman, Vice Chairman and members of the Board are elected at the Annual General Meeting.</p> <p>Proposals for the election of members of the Board of Directors are presented to the Annual General Meeting by a Nominations Committee, which comprises from three (3) to five (5) members who are named by the Board of Directors for a maximum of one year.</p> <p>3) Signing for the Company</p> <p>The company is signed for by the President & CEO alone, and members of the Board of Directors, two together.</p> <p>The Board of Directors may authorize other persons specified by name to sign for the company, two together or severally together with a member of the Board.</p> <p>The Board of Directors decides on procedures. Provision can be granted only if such a person, but the holders of procedures sign for the company two together or severally together with a member of the Board or another person authorized to sign for the company.</p> <p>4) Auditors</p> <p>The company shall have at least one (1) and no more than three (3) auditors. The auditor shall be an auditor or public accounting corporation approved by the Central Chamber of Commerce.</p> <p>The auditor shall expire at the termination of the Annual General Meeting following the election.</p> <p>5) Financial</p> <p>The company's financial year is the calendar year.</p> <p>6) Annual General Meeting</p>	<p>The Annual General Meeting shall be held once every year, within four (4) months of the end of the financial year, at a date determined by the Board of Directors.</p> <p>At the meeting shall be</p> <p>Presented:</p> <p>1. The financial statements, including the income statement, balance sheet and annual report, and the consolidated income statement and balance sheet.</p> <p>2. The auditor's report and any statement issued by the Board of Directors on account thereof.</p> <p>Resolved upon:</p> <p>1. The adoption of the income statement and balance sheet, and the consolidated income statement and balance sheet;</p> <p>2. Any resolution connected with the profit or loss shown in the adopted balance sheet and consolidated balance sheet;</p> <p>3. Discharging the members of the Board of Directors, and the President & CEO from liability; and</p> <p>4. The number of members of the Board of Directors and of auditors, and their remuneration.</p> <p>Resolved:</p> <p>1. Chairman, Vice Chairman and members of the Board of Directors; and</p> <p>2. The auditors; and</p> <p>Transmitted:</p> <p>1. Any other business specifically indicated in the notice of the meeting.</p> <p>Dated 23 November 2002</p> <p>Witness to the above signatures,</p> <p>Raymond Y. C. Tang, Arthur K. H. Chan & Co. 150 Floor, United Centre, No. 95 Queenway, Hong Kong, Solicitor & Notaries</p>
---	---

Figure 12.5-4. A copy of the students’ Article of Association.

12.6 INDOOR AIR QUALITY

Poor indoor air quality is the main culprit behind sick building syndrome (SBS) that describes a host of symptoms that include headache, nausea, dizziness, sore throat, dry and itchy skin, sinus congestion, nose irritation and fatigue. It is known to triggers and exacerbates allergies and asthma. Fisk and Rosenfeld [13] estimated the total costs of poor indoor air to US firms to be about US\$ 10-20 billions for sick building syndrome, US\$ 1-4 billions for allergies and asthma and US\$ 6-19 billions for other respiratory-related illnesses. A similar study conducted by the Hong Kong Environmental Protection Department revealed that about three percent of the salary loss is associated with poor indoor air [14], which is roughly equivalent to US\$ 0.15 billions each year.

Researchers found that indoor air quality (IAQ) is closely related to indoor activities, building, ventilation and furnishing materials and quality of outdoor air. IAQ survey carried out at nine local Hong Kong shopping malls showed that high occupancy and insufficient ventilation led to high level of carbon dioxide, while illicit smoking and poor ventilation at the food courts contributed to the substantially higher carbon monoxide and PM10 levels [15]. Domestic homes in Hong Kong also registered alarmingly high level of PM10. It was confirmed by a separate study that the respirable suspended particulates (RSP) and total suspended particulates (TSP) in Hong Kong residential buildings are significantly higher than most countries [16]. This is aggravated during cooking, smoking and incense burning. The ambient air pollution level in Hong Kong follows a seasonal trend [8]. Air pollution is less during summer because the prevailing shore wind helped dilute the air pollution, while in winter, a northerly synoptic airflow carried large amount of pollutants from the neighboring industrialized areas of Southern China.

Table 12.6-1 lists the common indoor air pollutants, their sources and health impacts. Information for indoor VOCs is listed in a separate Table 12.6-2. A summary of indoor air quality standards and guidelines for different countries is presented in Table 12.6-3.

Table 12.6-1. Sources and health impacts of common indoor air pollutants.

Indoor Air Pollutants	Sources	Health Effects
Respirable suspended particulates (PM ₁₀)	<ul style="list-style-type: none"> • tobacco smoke; • emissions from cooking and heating appliances; • burning incense. 	<ul style="list-style-type: none"> • respiratory irritation and infection; • aggravation of existing respiratory or cardiovascular disease; • nasal and eye irritations.
Volatile organic compounds (VOCs)	<ul style="list-style-type: none"> • cleaning agents, cosmetics, waxes, carpets and paints; • building and furnishing materials; • office equipments like laser printers and photocopiers. 	<ul style="list-style-type: none"> • irritation; • neurotoxic effects; • hepatotoxic; • carcinogenic
Biological contaminants (Viruses, bacteria, fungi, molds, insects)	<ul style="list-style-type: none"> • outdoors; • humans; • animals. 	<ul style="list-style-type: none"> • allergic reactions; • infectious diseases; • irritations; • toxic effects
Environmental tobacco smokes (ETS)	<ul style="list-style-type: none"> • tobacco smoke 	<ul style="list-style-type: none"> • irritation to mucous membranes; • chronic and acute pulmonary effects; • cardiovascular effects; • carcinogenic.
Formaldehyde (also a VOC)	<ul style="list-style-type: none"> • ETS; • building materials and fabrics; • cleaning fluids and adhesives. 	<ul style="list-style-type: none"> • irritation to eye, nose and respiratory system; • allergy; • carcinogenic.
Asbestos	<ul style="list-style-type: none"> • asbestos cement; • building materials like pipe lagging, ceiling tiles. 	<ul style="list-style-type: none"> • carcinogenic; • asbestosis (a scarring of lung tissues).
Radon and its decay products	<ul style="list-style-type: none"> • soils and rocks especially granite in HK; • building materials. 	<ul style="list-style-type: none"> • carcinogenic
Carbon monoxide	<ul style="list-style-type: none"> • combustion appliances; • cooking; • ETS. 	<ul style="list-style-type: none"> • headaches, flu-like symptoms, nausea, fatigue, chest tightness; • cardiovascular diseases; • death in high concentration.
Nitrogen oxides	<ul style="list-style-type: none"> • combustion appliances; • cooking; • ETS. 	<ul style="list-style-type: none"> • irritation of respiratory system and eyes; • decreased in pulmonary function in asthmatics; • decreased immune capacity, changes in anatomy and function of lung.
Ozone	<ul style="list-style-type: none"> • photocopiers; • laser printers. 	<ul style="list-style-type: none"> • irritation of eyes and respiratory tract; • damage lung tissue.
Sulphur dioxide	<ul style="list-style-type: none"> • combustion of fuels containing sulphur 	<ul style="list-style-type: none"> • decreased lung function in asthmatics

Table 12.6-2. Sources, odor threshold and health impact of common indoor VOCs.

Indoor VOCs	Sources	Odor Threshold (ppm) ¹	IARC Classification ²
Formaldehyde	Germicide, pressed-wood products, urea-formaldehyde foam insulation (UFFI), adhesives, paints, plastics, carpeting, gypsum board, ceiling tiles and panels, wood paneling.	0.83	2A
Benzene	ETS, solvents, paints, stains, fax machines, computer terminals, printers, water-based adhesives, carpets, plastics, synthetic fibres.	12	1
Carbon Tetrachloride	Solvents, refrigerant, aerosols, fire extinguishers, grease solvents.	96	2B
Trichloroethylene	Solvents, dry-cleaned fabrics, printing inks, paints, varnishes, adhesives, fax machines, computer terminals and printers, correction pen fluids, paint removers, spot removers.	28	2A
Tetrachloroethylene	Dry-cleaned fabrics, spot/textile cleaners, fax machines, computer terminals and printers.	27	2A
Chloroform	Solvents, dyes, pesticides, fax machines, computer terminals and printers, upholsteries, chlorinated water.	85	2B
1,2-Dichlorobenzene	Dry cleaning agent, degreaser, insecticides, carpets.	0.3	Inadequate data
1,3-Dichlorobenzene	Insecticide.	0.3	Inadequate data
1,4-Dichlorobenzene	Deodorant, mold and mildew control. Air fresheners/deodorizers, toilet bowl and waste can deodorizers, mothballs and mothflakes.	0.18	Inadequate data
Ethylbenzene	Styrene-related perfumes, synthetic polymers, solvents, fax machines, computer terminals and printers, furniture polish, latex and non-latex caulking compounds, floor tile adhesives, carpet tile adhesives.	2.3	Not classified
Toluene	Solvent, perfumes, detergents, dyes, water-based adhesives, moulding tape, wallpaper, calcium silica sheet, paint, carpeting, carpet adhesives, grease solvents.	2.9	3
Xylene	Solvent, dyes, insecticides, polyester fibres, adhesives, wallpaper, varnish, carpeting, wet-process photocopying, pressed-wood products, gypsum board, water-based adhesives, grease solvents, paints, carpet adhesives.	2.9	3

¹ AIHA, *Odour Thresholds for Chemicals with Established Occupational Health Standards* (1993).
² International Agency for Research on Cancer (IARC) Classifications:
Group 1: the agent is carcinogenic to humans (sufficient evidence of carcinogenicity in humans);
Group 2A: the agent is probably carcinogenic to humans (limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals);
Group 2B: the agent is possibly carcinogenic to humans (inadequate evidence of carcinogenicity in humans but sufficient evidence in animals);
Group 3: the agent cannot be classified as to its carcinogenicity to humans.

Table 12.6-3. Summary of indoor air quality standards and guidelines for different countries.

ITEM	Australia ^[1]	Canada ^[2]	China ^[3]	Hong Kong ^[4]	Japan	So. Korea	Singapore	UK ^[5]	USA ^[6]
Carbon monoxide	9 ppm	9 ppm	--	8000 µgm ⁻³	10 ppm	10 ppm	9 ppm	50 ppm	10 ppm
Carbon dioxide	1,000 ppm	1,000 ppm	--	1,000 ppm	1,000 ppm	1,000 ppm	1,000 ppm	5,000 ppm	2,000 ppm
RSP	--	150 µgm ⁻³	--	180 µgm ⁻³	0.15 mgm ⁻³	--	--	--	150 µgm ⁻³ [7]
TSP	90 mgm ⁻³	--	--	--	--	0.15 mgm ⁻³	--	--	--
Radon	200 Bq m ⁻³	--	200 Bq m ⁻³	200 Bq m ⁻³	--	--	--	--	--
Formaldehyde	0.1 ppm	0.1 ppm	0.08 ppm	100 µgm ⁻³	--	--	0.01 ppm	--	--
Nitrogen oxide	--	--	--	--	0.04-0.06 ppm	--	--	--	--
Nitrogen dioxide	--	--	--	150 µgm ⁻³	--	--	--	3 ppm	--
Ozone	0.12 ppm	--	--	120 µgm ⁻³	0.06 ppm	--	0.05 ppm	0.1 ppm	--
VOC	--	--	--	--	--	--	--	--	--
TVOC	500 mgm ⁻³	1 & 5 mgm ⁻³ [7]	0.5 mgm ⁻³	600 µgm ⁻³	300 mgm ⁻³	--	--	--	5000 µgm ⁻³
Temperature	--	floor/ceiling < 3 °C	--	20-26 °C	17-28°C	17-28°C	22.5-25.5 °C	--	--
Relative humidity	--	25-60%	--	30-60%	40-70%	40-70%	70%	--	65%
Air velocity	--	0.15-0.25 ms ⁻¹	--	0.25 ms ⁻¹	0.5 ms ⁻¹	0.5 ms ⁻¹	0.25 ms ⁻¹	--	--
Illumination	--	--	--	--	--	100 lux	--	--	--

^[1] Interim National Indoor Air Quality Goals recommended by NHMRC,
^[2] Make reference to ASHRAE, AIHA and ACGIH standards, and Air Quality in Office Buildings : A Technical Guide 1993,
^[3] Level 1 guideline for residential homes,
^[4] Standard Class recommended by the consultants in this IAQ study,
^[5] Occupational Exposure Limits: long-term exposure (8-h TWA period),
^[6] ASHRAE standards can be filled in instead,
^[7] ASHRAE indoor exposure guideline (24-hr average).

12.6.1 Indoor Air Survey

Indoor air survey was carried out for Hong Kong domestic homes, as there are no available data in this category at the time. A clear understanding of the local indoor air pollution problem is invaluable for the success of the product.

12.6.1.1 Site selection criteria

The measurement sites are private residential homes selected on the basis of (1) the prevalence of housing types, (2) proximity to residential centers and (3) accessibility. Homes that had been renovated within the last five years have higher VOC level and were not considered in this survey. Six sites were selected based on the above criteria, but only four were surveyed (Table 14) because of the unfortunate outbreak of SARS during this period. An exact record of the sites was assembled starting with the building location, age and state of repair along with the district information, proximity of neighboring buildings and local traffic conditions that affects the ambient air quality. The residents provided the floor plan, apartment conditions and furnishings, ventilation and schedule of indoor activities (Table 12.6-4).

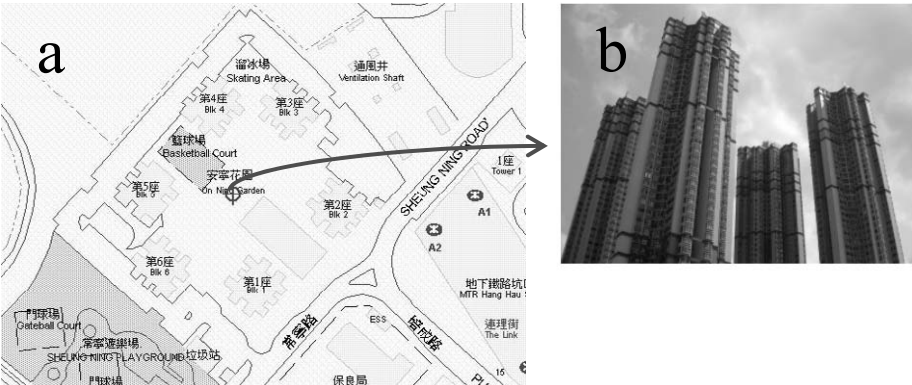
Table 12.6-4. Description of the sites chosen for indoor air survey

Site	District	District Condition	Type	Age	Floor	No. of Occupant	Pets	Cleaning Freq.	Stove	Fuel
1	Sai Kung	Residential, moderate population with low traffic flow	Villa	10 years	1/F	1	0	1/wk	Gas	LPG
2	Tseung Kwan O	Residential, high population with medium traffic flow	Private	17 years	22/F	4	0	>3/wk	Gas	Towngas
3	Kowloon Bay	Commercial and residential mix with a nearby construction	Private	18 years	28/F	4	Fish	2-3/wk	Gas	LPG
4	Clear Water Bay	Residential with low traffic flow	Private	6 years	7/F	4	0	1/wk<	Gas	Towngas

12.6.1.2 Site modeling

Site modeling was carried out using the commercial software, FEMLAB to investigate the airflow and pollutant dispersion in each household. Site 2 is an apartment located in the 22nd floor of a 17 years old residential block shown in Fig. 12.6-1. The floor plan and photos of the apartment are included in Fig. 12.6-2. The irregular-shaped floor plan is the norm rather exception in Hong Kong, where space is a premium. The floor plan was drawn using AutoCAD and exported to FEMLAB. The airflow patterns and pollutant dispersion shown in Fig. 12.6-3 were obtained by solving the general material and momentum balance equations and Fick's second Law [18]. The results show that the irregular apartment layout contributes to the complex flow pattern in the apartment. Stagnant air appears throughout the apartment where pollutants can accumulate. The modeling results were confirmed by experiment. Air pollution data at different locations in the apartment were obtained under different

ventilation conditions and the results were in good agreement with the pollution profile predicted by the model. The model was therefore used to guide the air



survey study.

Figure 12.6-1. (a) Map of the location and (b) photo of the residential block for site 2.

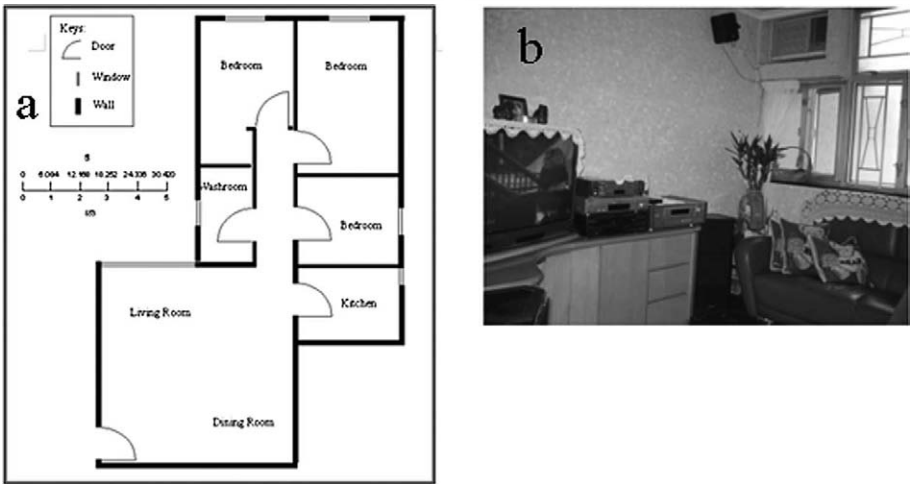


Figure 12.6-2. (a) Floor plan and (b) photo of the site 2 apartment.

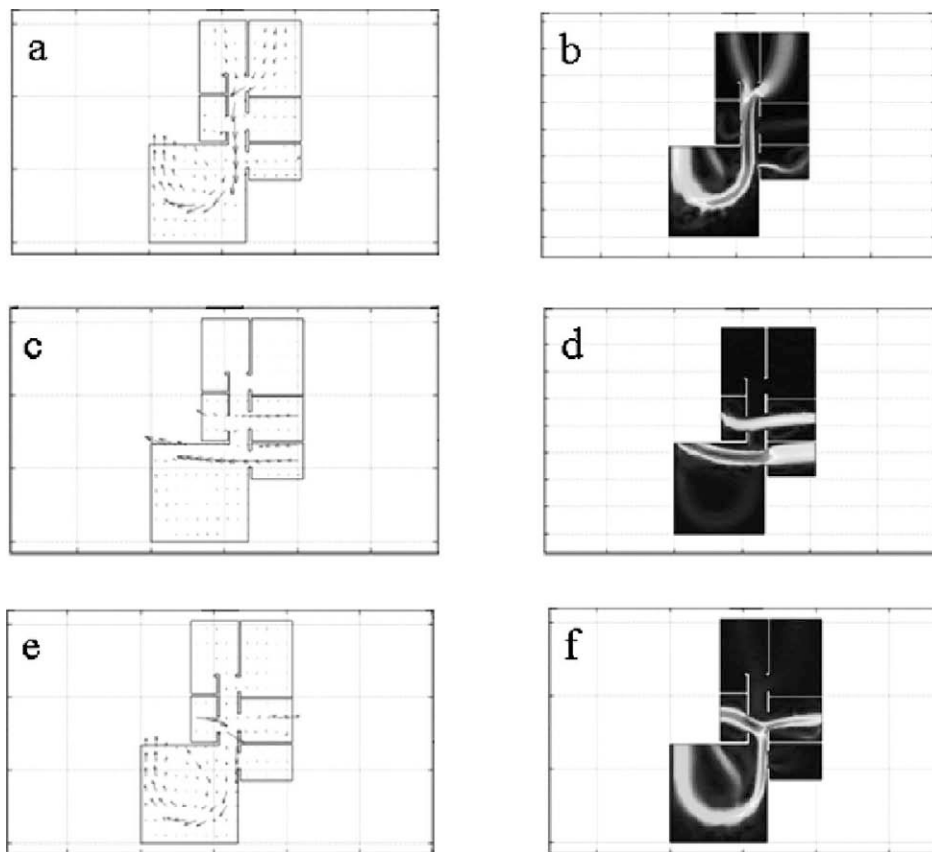


Figure 12.6-3. Airflow patterns and pollutant distributions in site 2 apartment with windows and doors open when the prevailing wind is from (a) & (b) north, (c) & (d) east and (e) & (f) west

12.6.1.3 Site air quality survey

Six common indoor air pollutants were selected based on their health impact, prevalence in Hong Kong and the availability of the right measurement equipments. They are the carbon monoxide (CO), formaldehyde (HCHO), total volatile organic carbons (TVOCS), aerosols (PM_{2.5}/PM₁₀), bioaerosols and carbon dioxide (CO₂). The carbon dioxide measurement was included as an indicator for the adequacy of ventilation. Measurements were conducted over a period of five days at each selected sites with the permission of residents. One day is needed to set up and calibrate the equipments. Real time monitoring of the temperature, humidity, aerosol, carbon monoxide, carbon dioxide and formaldehyde were conducted at each sites for the next 72 hours using equipments listed in Table 12.4-3. The air samplings for formaldehyde, TVOC

and bioaerosols were done when the residents were away from home to avoid inconvenience. The formaldehyde and total VOCs were sampled using sorbent tubes and analyzed in the Applied Technology Center (ATC) laboratory using gas chromatography. Airborne bacteria and fungal spores were sampled using Andersen-type bioaerosol impactor using tryptic soy agar (TSA) and malt extract agar (MEA) plates, respectively. The viable colonies were counted after sample incubation. The residents were interviewed on the last day before the equipments were disassembled and removed.

Table 12.6-5 summarizes the results of the indoor air quality survey conducted at each sites and compared to air quality standards recommended by the Hong Kong Environmental Protection Department for very good indoor air quality (Level 1). All four sites have relatively good ventilation and their eight hours average carbon dioxide levels were high but remain within the recommended value. The 8-hours average level of respirable suspended particles (RSP) at all four survey sites exceeded the HKEPD's level 1 recommendation. The high level of PM_{2.5} is a cause for alarm, as it is suspected to contribute to lung cancer. The sources of RSP are from nearby construction site and local traffic. Most originated from human activities such as cooking as the surges in the RSP level coincided with meal times. The airborne bacteria level is also high at all the sites, and despite conducting the sampling when residents were at work, site 3 & 4 exceeded HKEPD level 1 & 2 recommendations. This is found to correlate to the number of residents and their cleaning habits (Table 12.6-4). The carbon monoxide level is low for apartments with separate kitchen area, but at site 4 where the kitchen is attached to the living room, the carbon monoxide level is high and exceeds the recommended level when the residents were cooking. The formaldehyde, benzene, toluene and xylene levels are low as no recent renovations were done and all residents were nonsmokers. The survey results were in good agreement with a more detailed air quality survey of twenty Hong Kong apartment homes (Table 12.6-6) commissioned by the team with funding from the Hong Kong Innovation and Technology Commission.

The results of the air quality surveys and interviews with the residents indicated that dust, particulates and bioaerosols are major problems in Hong Kong residential homes. The high level of carbon monoxide produced during cooking must be addressed. Odors are the most common complaints from the residents despite the recorded low level of VOCs. This is understandable since the threshold odor for most of these compounds is very low. The team therefore recommends that the product should feature aerosols (i.e., dust and particulates), bioaerosols (i.e., airborne bacteria and fungi), carbon monoxide and odor (i.e., VOCs) removal technologies.

Table 12.6-5. Indoor air pollution at the four selected sites.

	Site 1	Site 2	Site 3	Site 4	HKEPD (level 1)
CO ₂ (ppm)	480	500	360	400	< 800
RSP (µg/m ³)					
PM ₁₀	80	110	115	120	< 20
PM _{2.5}	65	110	100	115	not available
CO (ppb)	30	50	100	1800	< 2000
HCHO (µg/m ³)	< 10	< 10	- -	< 10	< 100
Benzene (µg/m ³)	1	1.4	1.3	0.7	< 16.1
Toluene (µg/m ³)	0.9	4.8	4.6	3.8	<1092
Xylene (µg/m ³)	0.2	0.8	0.5	1.8	<1447
Bacteria (CFU/m ³)	480	440	1080	700	< 500

Table 12.6-6. Hong Kong indoor air quality survey.

Pollutants	Units	HKEPD IAQ-O (8 h)	Domestic Households (summer) ¹	Domestic Households (winter) ¹	Offices ²	Restaurant ²	Cinema ²	Shopping Mall ²
CO	µg/m ³	10,000	--	--	0.8	3.3	1.7	1.7
CO ₂	ppm	1,000	461	567	960	1271	1362	1002
HCHO	µg/m ³	100	77	14	71	162	140	39
RSP	µg/m ³	180	67	76	30	323	55	78
Benzene	µg/m ³	16.1	0.3	4.8	6.6	12.2	1.85	5.8
m-dichlorobenzene	µg/m ³	500	21.9	5.8	2.8	0.9	1.8	1.5
Ethylbenzene	µg/m ³	1447	1.8	6.5	20.4	7.7	3.8	8.3
Tetrachloroethylene	µg/m ³	250	5.4	9.8	3.0	5.6	1.6	1.9
Toluene	µg/m ³	1092	19.7	17.4	250	104	7.6	86
Trichloroethylene	µg/m ³	770	not measured	not measured	29.2	1.02	0.5	2.7
o-Xylene	µg/m ³	1447	3.7	8.3	15.0	8.6	0.6	7.6
m, p-Xylene	µg/m ³	1447	2.7	4.2	35.9	22.9	17.9	18.8
bacteria	cfu/m ³	1000	134	796	740	1002	430	2140
fungi	cfu/m ³	500	not measured	not measured	187	77	26	380

¹Indoor air pollution survey carried out with founding from HK ITC and contracted to Acron International Technologies, Inc.
²data based on survey conducted by EHS Consulting Ltd Agreement # CE 14/95

12.7 CATALYST AND ADSORBENT

Filtration is an efficient and inexpensive method for removing dust, particulates and bioaerosols from indoor air. High efficiency filters can remove up to 95 % of airborne particles as small as 0.3 microns. However, odor associated with gaseous VOCs cannot be removed by simple filtration and must be captured using adsorbents such as activated carbon and charcoal. Frequent replacement is needed since these adsorbents have finite capacity and cannot be regenerated. The aim of this project is to develop an effective remediation technology for common airborne VOCs found indoor.

12.7.1 Catalyst Formulation

An efficient, low temperature oxidation catalyst was developed based on highly disperse metal catalyst on nanostructured TiO_2 support. The nanostructured catalyst proved to be resistant to most common poisons found in the environment including halogen- and sulfur-containing compounds. The addition of vanadium oxide dopant promotes the catalytic activity, inhibits metal sintering and prevents deactivation [18]. A simple factorial design was used to guide the catalyst research. Table 12.7-1 lists the experimental variables and their value range.

Table 12.7-1. Experimental variables for catalyst research

Experimental Variables	(-)	(+)
TiO_2 support (11 nm)	hydrothermal	thermal
Vanadium oxide	monomeric	polymeric
Metal	Metal 1	Metal 2
Metal loading (wt.%)	0.1	1

12.7.2 Catalyst preparation and characterization

The 11 nm-sized TiO_2 were crystallized using either hydrothermal or thermal methods from 100 nm, amorphous gel spheres. The TiO_2 crystal and agglomerate sizes were determined by X-ray diffraction (Philip 1080) and transmission electron microscopy (JEOL JEM 2010), respectively. The surface area and chemistry of the nanostructured TiO_2 were analyzed by nitrogen physisorption (Coulter SA 3100) and Fourier transform infrared spectroscopy (FTIR, Perkin-Elmer GX 2000). Metal catalyst was deposited by incipient

wetness method from salt precursor. A low and high metal catalyst loading of 0.1 and 1 weight percents were prepared. Low temperature ozone pretreatment was used to decompose the salt precursor and obtain well-dispersed metal catalysts. Monomeric or polymeric vanadium oxide was then deposited. The overall composition of the prepared catalyst was determined by inductively coupled plasma, atomic emission spectrometer (ICP-AES, Perkin Elmer Optima 3000XL) after acid digestion, while its surface composition was analyzed by X-ray photoelectron spectroscopy (XPS, Physical Electronics PHI 5000). The metal catalyst and dopant dispersions were established by carbon monoxide chemisorption (Altamira Instruments AMI-200) and micro-Raman spectroscopy (Renishaw Raman microscope 160).

12.7.2.1 Catalyst optimization

Catalysts were tested for oxidations of carbon monoxide and toluene. The tests were carried out in a differential reactor shown in Fig. 12.7-1 and analyzed by an online gas chromatograph (HP 6890) equipped with thermal conductivity and flame ionization detectors. Gases including dry air and carbon monoxide were feed to the reactor by mass flow controllers, while the liquid reactant, toluene was delivered by a syringe pump. Thermocouple was used to monitor the catalyst temperature. Catalyst screening and optimization identified the best catalyst formulation with a conversion rate for carbon monoxide and toluene at room temperature of 1 and 0.25 mmole¹g⁻¹min⁻¹. Carbon monoxide and water were the only products of the reactions.

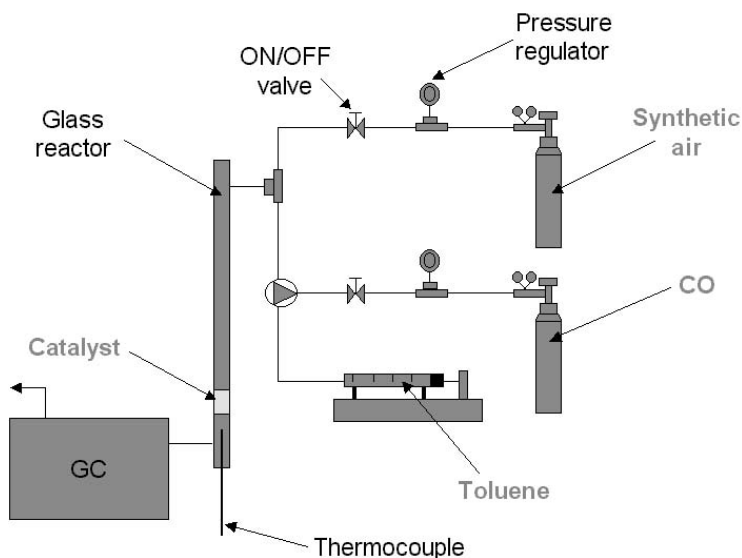


Figure 12.7-1. Schematic diagram of the reactor set-up for catalyst performance test.

12.7.3 Adsorbent Formulations

12.7.3.1 VOCs adsorbent

A regenerable adsorbent for VOCs capture was prepared by chemical and structural modifications of mesoporous silica, MCM-41. The adsorbent has a large adsorption capacity for VOCs, fast adsorption rate, excellent regenerability (i.e., low regeneration temperature and fast regeneration) and superior hydrothermal stability. The MCM-41 powder was prepared from an alkaline synthesis solution containing tetraethyl orthosilicate (TEOS, 98%), cetyltrimethylammonium bromide (CTABr, 99.3%) and ammonium hydroxide (NH_4OH , 28–30 wt.%) at a molar ratios of 6.58 TEOS: 1 CTABr: 292 NH_4OH : 2773 H_2O . The synthesis was conducted at room temperature under vigorous mixing to obtain well-dispersed, micron-sized particles. The MCM-41 was filtered, washed, dried and ground to obtain free flowing powder. The powder was collected and calcined in a single batch at 823 K for 24 h to burn away the organic templates. The MCM-41 was subjected to chemical and structural modifications. The particle size of MCM-41 was determined by scanning electron microscopy (SEM, JEOL JSM 6300F). A detailed description of the particle morphology and pore structure was obtained using a high resolution, transmission electron microscope (TEM, JEOL JEM 2010), while the average surface area and pore size were calculated from nitrogen physisorption experiments (Coulter SA 3100) and X-ray diffraction data (XRD, Philip 1080).

The modified MCM-41 adsorbents were coated on a monolith and tested in a flow cell shown in Fig. 12.7-2. A pressure regulator and a flowmeter were used to adjust the airflow to a saturator containing the target volatile organic compound. A separate air stream was used to dilute and control the concentration of the feed VOCs. VOC sensors located at the flow cell inlet and outlet were used to monitor airborne VOC concentrations. Figure 12.7-3 depicts the results of a typical experimental run involving VOC adsorption at ambient temperature and regeneration at 423 K. The adsorption capacity, adsorption rate and regeneration rate were determined. The best adsorbent has adsorption capacities for ethanol, acetone and oil of 0.4, 0.8 and 10g per gram of adsorbent. The adsorption and regeneration are rapid and are often completed within 5 minutes.

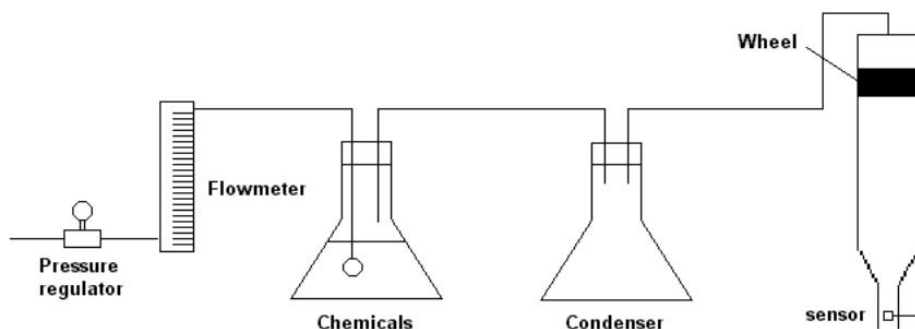


Figure 12.7-2. Schematic diagram of the reactor set-up for adsorbent performance test.

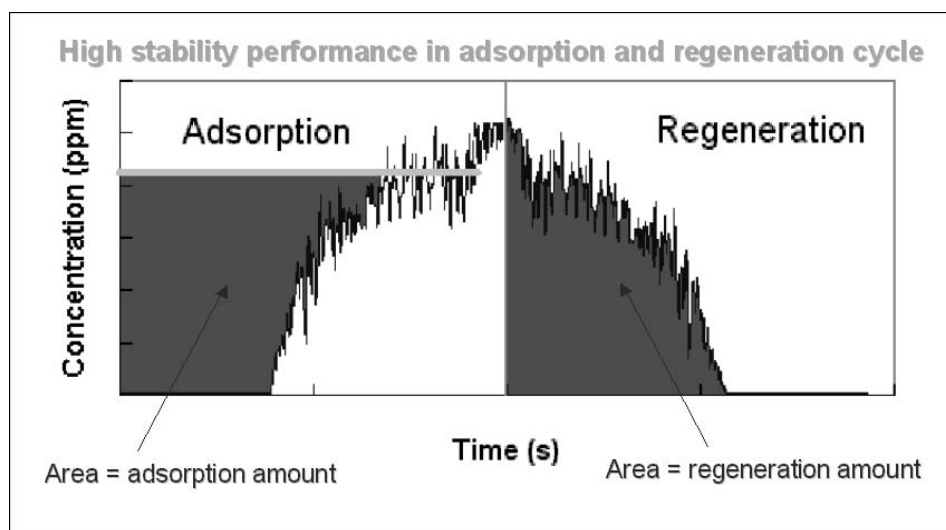


Figure 12.7-3. Typical experimental data from an adsorption experiment.

12.7.3.2 Desiccant

A new desiccant formulation was prepared from a mixture of submicron-sized silica gel and molecular sieves to achieve the best combination of large water capacity, rapid moisture adsorption and easy regenerability. The formulation also tolerates the presence of VOCs and smokes. Commercial NaX and silica gel were crushed and mixed in the proportion of 1:2 and wash coated on a monolith for testing. The same test cell shown in Fig. 12.7-2 was used. The airflow to the saturator was adjusted to obtain the desired humidity in the feed air. Humidity sensors located at the flow cell inlet and outlet, were used to

monitor the moisture content of the air. The adsorption capacity of the desiccant mixture was about 0.7 g/g with an adsorption rate of $1.2 \text{ g}^1\text{g}^{-1}\text{min}^{-1}$ and a regeneration rate of $0.7 \text{ g}^1\text{g}^{-1}\text{min}^{-1}$ at 423 K .

12.7.4 Catalyst-adsorbent monolith wheel

A powder formulation containing the appropriate amounts of catalyst, adsorbent and desiccant will be formed into a monolith. Monoliths are characterized by low-pressure drop and large geometric surface area. The open channel structure makes monolith less susceptible to fouling. Ceramic monoliths with cell densities of 25 to 1600 cells per square inch (i.e., cell sizes of 5 - 0.6 mm) are routinely made by extrusions. The process involves powder blending, pugging, extrusion, cutting, drying and sintering to produce the final monolith. Powder preparation is considered to be the most critical step in monolith forming. The catalyst being sensitive to many of the chemical additives and processing steps used in the extrusion process would be separated coated onto the prepared monolith. The adsorbent and desiccants are of different sizes and proper mixing, grinding and screening are needed to produce a free-flowing powder of narrow particle size distribution. Particle sizes larger than 5 microns are not suitable for extrusion. Computer software loaned by Prof. K.M. Ng groups provided a guide for powder processing. The recommended process for obtaining 2 microns powder is shown in Fig. 12.7-4. Suitable binder, surfactant, deflocculant, coagulant, lubricant, plasticizer, and preservative are needed to prepare an extrudable mixture. Unfortunately, the high cost of extrusion die prevented the team from producing their own monolith, instead commercial desiccant monoliths were purchased and coated with the low-temperature catalyst and regenerable VOC adsorbent.

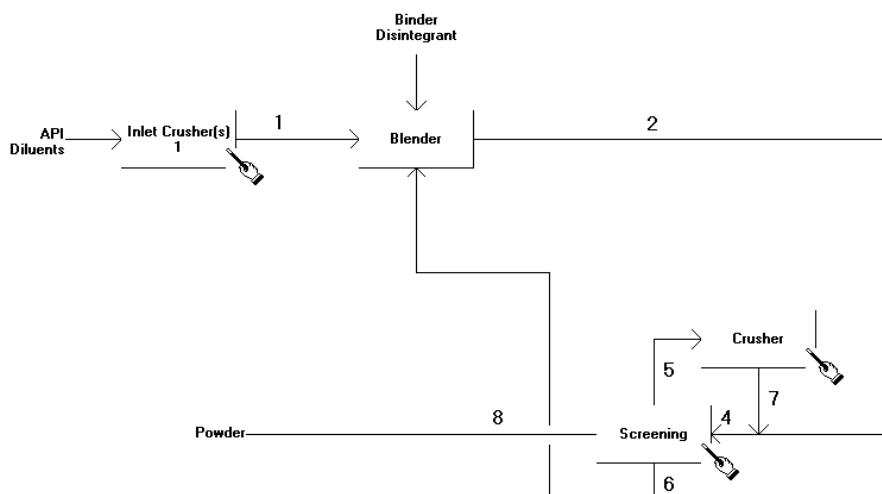


Figure 12.7-4. Schematic diagram for powder processing.

12.8 PROTOTYPE DESIGN

A. Rational Design Approach

Cross [19] advocates a rational approach in the design process. He described in his book the seven steps procedure for the “rational method for new design” shown in Fig. 12.8-1 and listed in Table 12.8-1. The method covers every aspects of the design process from problem clarification to detailed design. It also facilitates better teamwork and enables better task subdivision. The project team employed this method to guide the design of the indoor air quality control appliance.

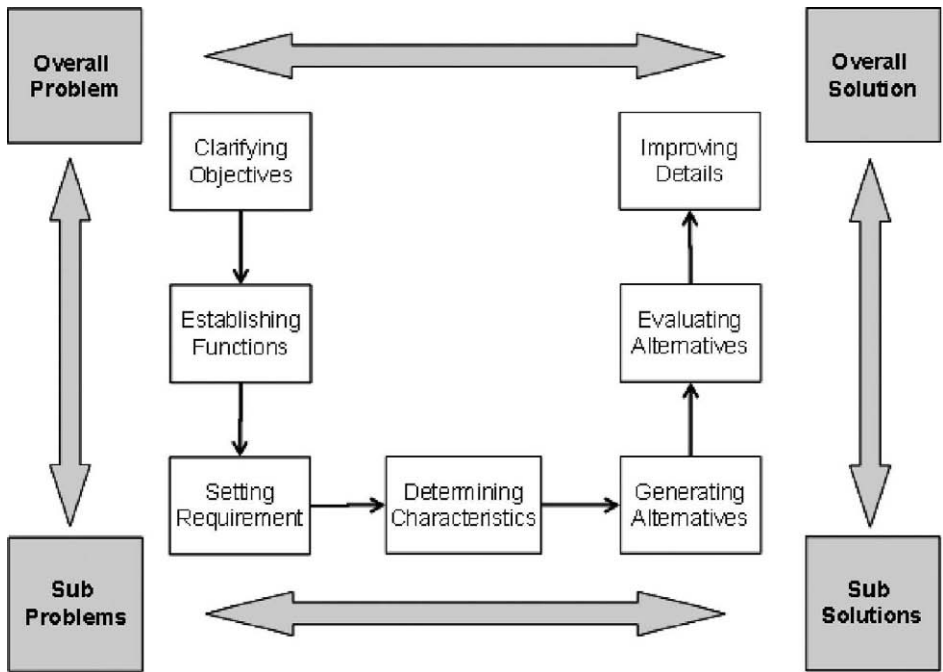


Figure 12.8-1. Schematic of the rational method for new design [20].

12.8.1 Clarifying Objectives

The project team’s main objective is to design an efficient indoor air quality control appliance that can achieve the most stringent IAQ standard using new and competitive catalyst and adsorbent technologies. The appliance must be

safe, reliable, user-friendly and cost-competitive. This is summarized in the objective tree shown in Fig. 12.8-2.

Table 12.8-1. Rational method for new design [20]

Stage	Design Stage	Design Objective
1	Objective Tree	clarify design objectives and sub-objectives, and their relationships
2	Function Analysis	establish the required function and system boundary of the new design
3	Performance Specification	create an accurate performance specification required by the design solution
4	Quality Function Deployment	set targets for the engineering characteristics of the product that satisfy the customers' requirements
5	Morphological Chart	generate a complete range of alternative design solutions in order to broaden the search for potential new solutions
6	Weighted Objectives	assess the added value of each design proposal based on different weighted objectives
7	Value Engineering	increase or maintain the value of the product to its customer, while reducing its production cost

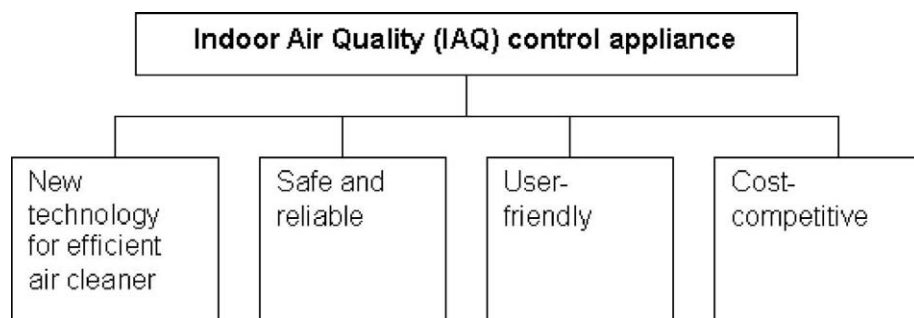


Figure 12.8-2. Objective tree for indoor air quality control appliance.

12.8.2 Establishing Functions

The indoor air quality appliance must have better than ninety percent efficient in removing airborne particulates, bioaerosols (i.e., airborne bacteria and fungi spores), carbon monoxide, volatile organic compounds and odors. It must meet or exceed the industry's standards in performance and safety. The product must be able to maintain the pollutants in indoor air at below government IAQ standards and must not emit or produce harmful secondary pollutions during

operation. The manufacturing cost should not exceed US\$100 and preferably within US\$50 per units.

12.8.3 Setting Requirements

Next, the team identified the performance, safety, customer, marketing and manufacturing requirements for the indoor air quality control appliance.

12.8.3.1 Performance requirements

1. removes better than 95 percent of airborne particles and microorganisms with sizes down to 0.3 micron,
2. converts carbon monoxide up to 5000 ppm, into harmless carbon dioxide,
3. removes better than 90 percent of volatile organic compounds (VOCs) up to 30 ppm and better than 50 percent of VOCs up to 200 ppm,
4. converts VOCs into harmless carbon dioxide and water,
5. kills and inactivates better than 50 percent of airborne bacteria and fungi spores,
6. converts inactivated bacteria and fungi spores into harmless carbon dioxide and water,
7. deodorizes air of tobacco and incense smokes, cooking odors and others,
8. dehumidifies the air at a rate not less than 10 L/day at 20°C and 80 percent relative humidity,
9. cleans and dehumidifies a room size not smaller than 20 m²,
10. maintains a clean air delivery rate (CADR) not less than 50 cfm,
11. power consumption not to exceed 200 W,
12. design life of at least 10,000 h (i.e., 4.5 years),
13. light and portable with weight not exceeding 10 Kg.

12.8.3.2 Safety requirements

1. complies with industry safety standards,
2. must not contain any hazardous materials and all materials must be clearly identified,
3. includes redundant safety features and intelligent control devices to ensure safe and optimal performance,
4. simple user friendly operation with clearly labeled instructions.

12.8.3.3 Customer requirements

1. cleans, disinfects and deodorizes indoor air,
2. delivers clean and comfortable air on demand or automatically,
3. low cost,
4. simple user friendly operation with smart automatic functions,
5. minimal upkeep and maintenance,
6. built-in air quality monitoring and display
7. smart and attractive appearance,

8. portable and compact design,
9. silent operation,
10. energy efficient and environmentally-friendly manufacturing and materials.

12.8.3.4 Marketing requirements

1. high efficiency air cleaner for particulate, allergen, pathogen, odor and VOC removal and remediation,
2. product certification, independent laboratory tests and customer's testimonial,
3. new proprietary or breakthrough technology that differentiate the product from the competitors,
4. potential to generate a new series of product lines,
5. extra functional features and add-ons,
6. user-friendly and smart features
7. attractive and compact design,
8. competitive pricing.

12.8.3.5 Manufacturing requirements

1. minimize the number of major component parts,
2. lower production cost by subcontracting the design and manufacture of major component parts (e.g., heater, blower, fan, control panels, power supply, etc.),
3. keep the assembly process simple with no more than 15 steps,
4. manufacture the core technology in-house to keep better quality assurance,
5. employ environmental friendly manufacturing approach using recycled materials and easily recyclable component parts,
6. maintain a clean and safe working environment,
7. build a production line with capacity of at least 1000 units per months.

12.8.4 Determining characteristics

The indoor air quality control appliance consists of air handling, filtration, purification and dehumidification systems. Mr. Peter Chan of Chiaphua Industries Ltd. was closely consulted in completing the engineering specifications for the product.

12.8.4.1 Air handling system

An air inlet area of at least 400 cm² and a louvered exit of 75 cm² are recommended for target capacity and physical size of the appliance. The efficient and quiet centrifugal fan unit is popularly used in air conditioners and air purifiers. It costs less than the other fan units of similar size and is easy to install and assemble. A fan with adjustable air deliver rate of 0 to 250 cfm will be used to draw air through the air filter, dehumidifier and purifier units. A smaller fan with air delivery rate of up to 10 cfm is needed for the regeneration

air stream. The air is heated by electric heating coil (100 W) that is safe and easy to control. A simple thermostat and control circuit to prevent overheating and cuts heater power when fan is accidentally turned-off. A simple programmable logic circuit for the heater system can reduce the energy consumption by more than sixty percent and incorporate safety programming to minimize temperature spikes during shut-down. The hot air will be channeled and mixed will cool air before discharge.

12.8.4.2 Air filtration system

Airborne particles, bacteria, fungi spores and allergens will be removed by air filtration, which is often cheaper and more effective than electrostatic precipitators and ionizers. A disposable, high-efficiency filter capable of removing at least 95 percent of particles with size down to 0.3 micron will be installed. A washable coarse filter that removes fifty percent of particles larger than 10 microns will be used as a pre-filter to extend the life of the high efficiency filter by at least a third. An inexpensive sensor will be included to indicate when filter replacement is necessary.

12.8.4.3 Air purification system

Today, adsorption by activated carbon, charcoal and permanganate-coated alumina is the most common method for odor and VOCs removal. However, the adsorbent can become quickly saturated and may require frequent replacement. UV-activated photocatalytic oxidation (PCO) is popular in Japanese air purifier and is proven to be effective in odor removal. However, PCO reaction is slow and byproducts are often formed. This project introduces the use of regenerable adsorbent based on modified mesoporous silica and an efficient low temperature VOCs oxidation catalyst for VOCs removal and conversion into harmless carbon dioxide and water. The catalysts and adsorbents are coated on a honeycomb wheel that rotates at less than 20 revolutions per hour (rph). Seventy percent of the honeycomb area is exposed to incoming air at any given time, while the remaining area is undergoing high temperature (i.e., up to 100°C) regeneration. Calculation indicates that at least 8 g of adsorbents and 0.5 g of catalysts are needed to maintain a better than 90 percent removal of VOCs up to 30 ppm concentration.

12.8.4.4 Air dehumidification system

There are several desiccant-based, sorption dehumidifier designs in the market. Two commercial designs are illustrated in Fig. 18. The basic sorption dehumidifier shown in Fig. 12.8-3a has the advantage of simplicity in design, but air temperature leaving the unit can be as high as 40°C. A compressor-assisted unit (Fig. 12.8-3b) has higher capacity and lower temperature but is more complex and expensive. Desiccant wheels made of silica gel, zeolites and activated alumina can be purchased in a wide-range of shapes and sizes. A NaX zeolite honeycomb wheel of 217 mm diameter and 21 mm thickness is

necessary to remove 10 L of water per day when the room conditions are 20°C and 80 percent relative humidity. A quiet, high torque universal motor will be used to rotate the wheel at variable speed of up to 20 rph. At any one time, seventy percent of the wheel will be adsorbing moisture, while the remaining thirty percent is being regenerated. The hot airstream used in regeneration is channeled to an air-cooled condenser where the water is condensed and collected in a tank for later disposal. A simple water level indicator will be installed to give warning and stop the unit when the tank is full.

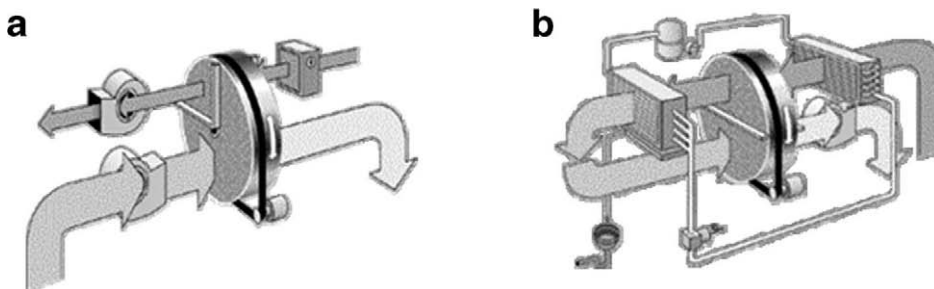


Figure 12-8.3. Schematic drawing of (a) basic sorption dehumidification process and (b) compressor-assisted air dehumidification process.

12.8.4.5 Other specifications

The size of the unit must not be bigger than 0.25 m (*w*) x 0.25 (*d*) x 0.35 m (*h*), which are the dimensions of common air purifiers of similar capacity. The appliance must weigh less than 10 Kg and should have lockable caster wheels for ease of transport around the house. An ergonomic and user-friendly read-out and control units will be provided to indicate the room's air quality and appliance operation.

12.8.5 Generating alternatives

Brainstorming sessions were conducted during the course of the product design. Each team was encouraged to pre-work the design problem along the stated objectives and requirements before the sessions. The sessions included all the team members and were guided by a guest moderator from industry. After each session, the ideas were grouped, categorized and discussed. The best design features were kept and refined before incorporating into the overall design. From these sessions, the prototype design team was able to propose ten viable, alternative appliance designs of which three will be discussed in detail.

12.8.5.1 Product design 1

The design employs filters for particulate removal, a desiccant wheel for air dehumidification and a catalyst-adsorbent wheel for air purification. Dehumidification discourages microbial growth in particular mildews and fungi. It also safeguards the performance of the catalyst-adsorbent wheel by removing moistures that may interfere with the catalyst and adsorbent. The use of two wheels design solves material compatibility problems and allowed independent performance optimization. However, the design is complicated and expensive.

Figure 12.8-4 displays a schematic flow diagram of the product design 1. The air is drawn-in through a washable, coarse filter (1) that removes particles larger than 10 microns and a disposable high efficiency filter (2) that removes 95 percent of particles with size down to 0.3 microns. The filtered air flows through a desiccant wheel (3) decreasing the relative humidity of the air to below 50 percent. A second set of wheel (4) coated the low temperature VOCs oxidation catalyst based on nanostructured catalyst converts organic pollutants into harmless carbon dioxide and water at ambient temperature. The wheel was also coated with regenerable VOCs adsorbent made from modified mesoporous silica to capture excess VOCs. The clean, dry air leaving the catalyst-adsorbent wheel flows past the air-cooled condenser before leaving the unit.

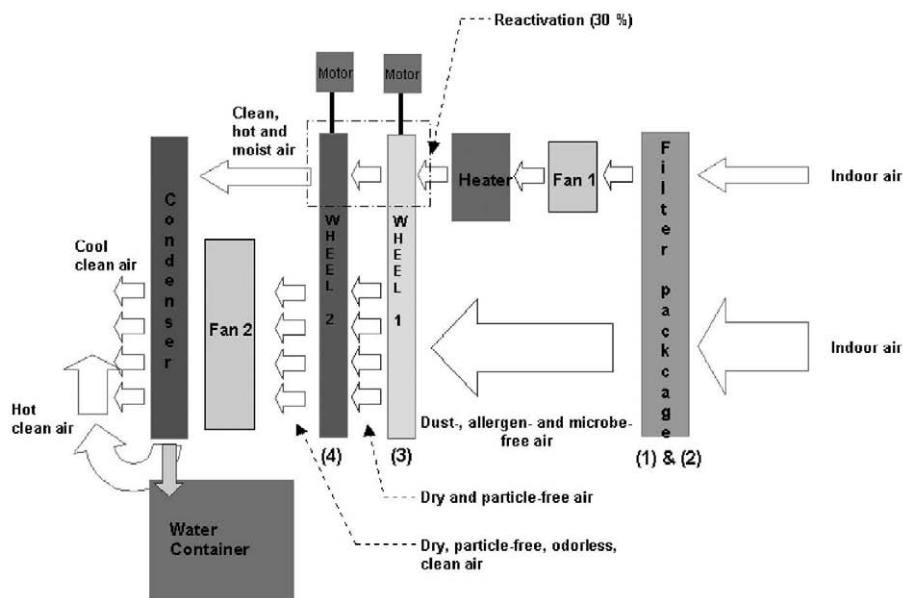


Figure 12.8-4. Schematic flow diagram for the product design 1.

A second stream of air with flow rate one-twentieth of the main airstream was heated and used to regenerate the catalyst-adsorbent and desiccant wheels. The heated air desorbs the organic pollutants captured in the adsorbent. The elevated temperature increases the catalyst activity enabling complete oxidation of the desorbed VOCs. The heated air then enters the desiccant wheel desorbing the adsorbed water and regenerating the desiccant. The hot, moist air is guided into an air-cooled condenser where water is condensed and collected in a reservoir pan. The two air streams are mixed and guided through a baffle before exiting the unit.

12.8.5.2 Product design 2

The design employs filters for particulate removal, a desiccant-VOCs adsorbent wheel for simultaneous air dehumidification and purification. The catalyst was coated on a separate sleeve directly across the hot air stream. This design eliminates the need for separate wheels and is both cheaper and simpler to manufacture. The higher temperature and pollutant concentration in the regeneration stream mean higher catalyst activity. However, the small flow rate and high moisture content of the regeneration stream can result in a poorer overall performance.

Figure 12.8-5 displays a schematic flow diagram of the product design 2. The air is drawn-in through a washable, coarse filter (1) that removes particles larger than 10 microns and a disposable high efficiency filter (2) that removes 95 percent of particles with size down to 0.3 microns. The filtered air flows through a desiccant-VOCs adsorbent wheel (3) decreasing the relative humidity of the air to below 50 percent and the airborne VOCs content to below IAQ standard. The clean, dry air leaving the desiccant-VOCs adsorbent wheel flows past the air-cooled condenser before leaving the unit. A second stream of air with flow rate one-twentieth of the main airstream was heated and used to regenerate the desiccant-VOCs adsorbent wheel. The heated air desorbs the water and organic pollutants adsorbed in the desiccant and adsorbent. The hot, moist air containing desorbed organic pollutants flows through a ceramic sleeve coated with the low temperature VOCs oxidation catalyst. The cleaned air is guided into an air-cooled condenser where water is condensed and collected in a reservoir pan. The two air streams are mixed and guided through a baffle before exiting the unit.

12.8.5.3 Product design 3

The design employs filters for particulate removal, a single desiccant wheel coated with both low temperature VOCs oxidation catalyst based on nanostructured catalyst and regenerable VOCs adsorbent made from modified mesoporous silica. The distribution of the active elements along the wheel thickness was optimized and shown in Fig. 12.8-6. The adsorbents are coated along two-thirds of the wheel thickness and all catalysts are concentrated on one

face of the wheel away from the entry point of the main airstream. This is a simpler design using less component parts and therefore cheaper to manufacture. It also allows easy conversion of existing commercial desiccant dehumidifier appliances into efficient air purifiers.

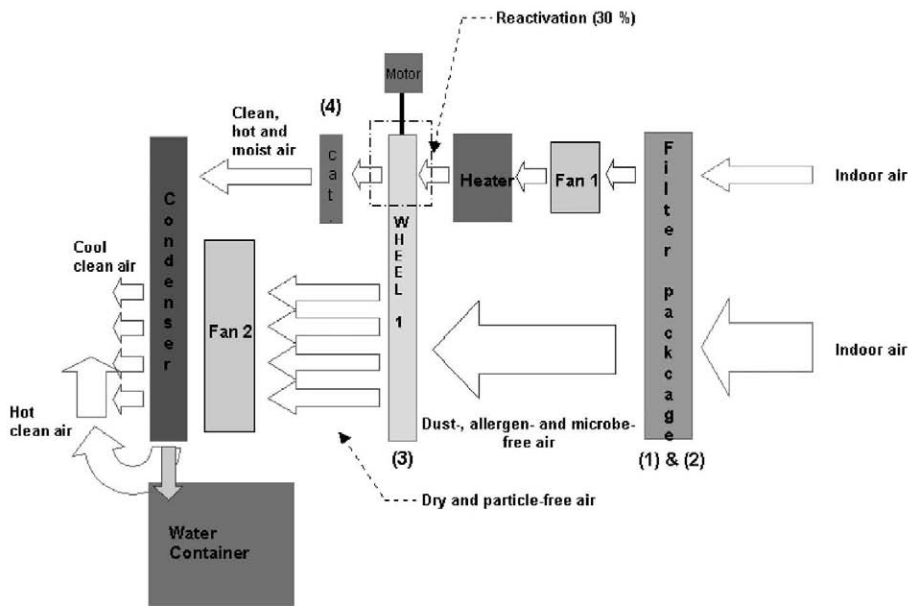


Figure 12.8-5. Schematic flow diagram for the product design 2.

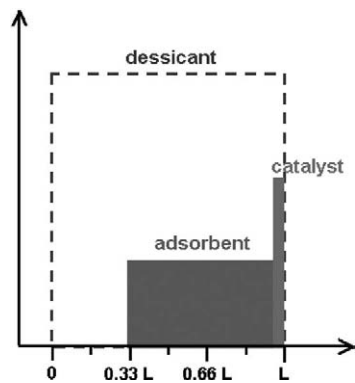


Figure 12.8-6. Schematic drawing of the active element distributions along the wheel thickness.

Figure 12.8-7 displays a schematic flow diagram of the product design 3. The air is drawn-in through a washable, coarse filter (1) that removes particles larger than 10 microns and a disposable high efficiency filter (2) that removes 95 percent of particles with size down to 0.3 microns. The filtered air flows through a wheel containing desiccant, VOCs adsorbent and nanostructured catalyst. Water was removed first as the air flows past the desiccant, then the VOCs is removed by the adsorbent and catalyst. Concentrating the catalysts and adsorbents near the exit face of the wheel make certain that during regeneration all desorbed VOCs are effectively converted into harmless carbon dioxide and water. The hot clean air then desorbs the water and regenerates the desiccant before flowing through an air-cooled condenser where water is condensed and collected in a reservoir pan. The two air streams are mixed and exit the unit at near room temperature.

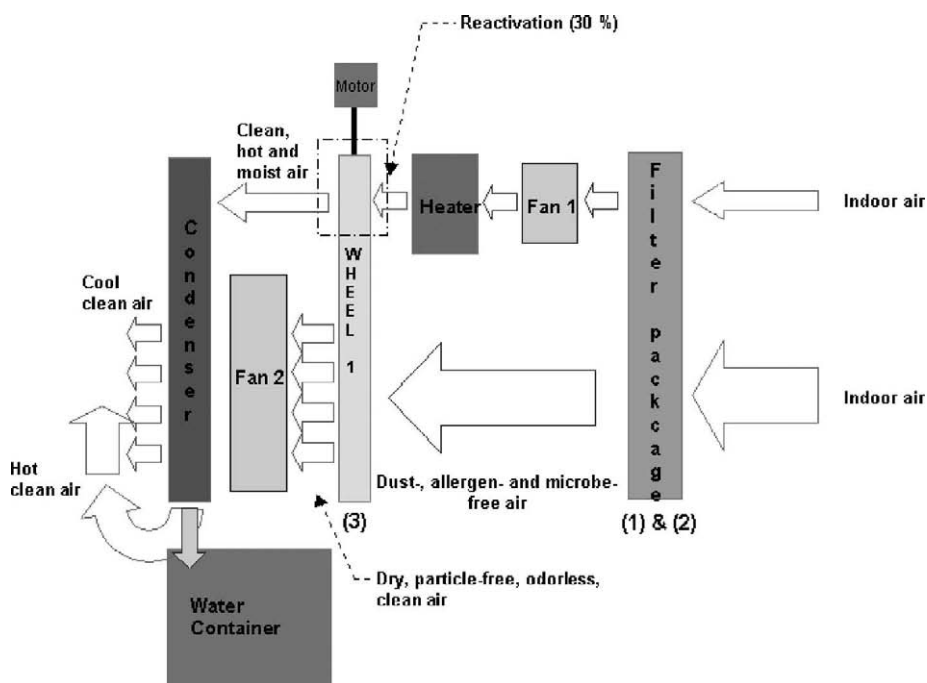


Figure 12.8-7. Schematic flow diagram for the product design 3.

12.8.6 Evaluating Alternatives

Only three of the stated objectives (Fig. 12.8-2) are relevant for this assessment phase. They are (1) air purification performance (50 %), reliability (25 %) and cost (25 %). In the absence of hard data, the members of the project team were

asked to rate each of the alternate designs relying on their own practical intuition. The industrial and faculty guests were also invited to participate in the process. The three highest ranked designs were discussed in the previous section. Despite the more complicated design and higher cost of the product design 1, it was believed to have better performance features than the other two designs.

12.8.7 Improving Details

The preliminary cost analysis was conducted with the help of Mr. Peter Chan of Chiaphua Industries Ltd. Table 12.8-2 compares the cost of subcontracting the manufacture of plastic and metal appliance components versus manufacturing in-house for a production volume of 1000 units per month. All calculated costs are below the US\$ 100 limit. A cost saving of twenty percent was forecasted assuming that the facility will be built and operated in China where the land and labor costs are cheaper.

Once the detailed dimensions and possible arrangements of the components were known, the appliance size and dimension can be determined. The students conducted a detailed design of the appliance's external casing using **SolidWorks® 2001**, a commercial mechanical design automation software, for detailed design of the appliance. The software makes it possible to quickly sketch ideas, experiment with features and dimensions and produce models and detailed drawings. The best arrangement places the air intakes along the sides of the appliance and the air exits at the top. A retractable water bucket with transparent window allow easy water disposal. Casters and retractable handles are included to improve mobility. These criteria were included in the final design and a 3D model was generated using the software and exported to a Rapid Prototyping Machine in HKUST's department of Industrial Engineering and Engineering Management to produce a quarter-size model of the finished product. The details of this process are illustrated in Fig. 12.8-8.



Figure 12.8-8. Using computer-aided design software and rapid prototyper to create product from a design blueprint.

Table 12.8-2. Estimated production cost.

Components	Subcontract/Assembly (US\$)		Manufacture (US\$)	
	Design 1	Design 3	Design 1	Design 3
Plastic housing and parts Upper and bottom bodies Water tank Bottom wheel support Motor support and assembly Fan blades Fan covers	16.00		6.50 ¹	
Metal components Condenser Screw and others	7.50		3.00 ¹	
Wheels Desiccant wheel Catalyst-adsorbent wheel	17.00	11.00	11.00 ¹	8.00 ¹
Electrical and electronics Sensor and logic controller Displays Motors Heaters Power supply Electrical cord	25.00		25.00 ²	
Packing Gift box and master cartoon Foam blocks Instruction manual Poly bag	2.50		2.50 ²	
Labor and other costs	4.00		8.00	
Value Engineering	72.00	66.00	56.00	53.00

¹Equipment and operating costs were included with exception of labor cost.²It is more efficient to subcontract electrical and electronic components and packaging materi

B. Assembly and Test of Prototype Units

In order to produce a functional prototype unit within the remaining three month of the project, two commercial desiccant-based dehumidifier appliances (Zojirushi's RV-D60-HC) were purchased from Japan in March 2003. The

appliances were disassembled and component parts were borrowed for the construction of the prototype indoor air quality control appliance.

12.8.8 Prototype Unit Design 1

Two honeycomb wheels were borrowed from the dehumidifier appliances for constructing the prototype design 1. The desiccant wheels contain NaX zeolite that adsorbs moisture but not VOCs. One of the wheels was coated with 12 grams of active formulation containing the modified mesoporous silica adsorbent and low temperature oxidation catalyst. The borrowed component parts were reassembled as shown in Fig. 12.8-9a. The wheel housing has to be modified and reconstructed to contain both wheels. A temporary external casing was used (Fig. 12.8-9b) before the final prototype was built. Airtight channels and seals for the hot air stream between the two rotating wheels were difficult to design and fabricate.

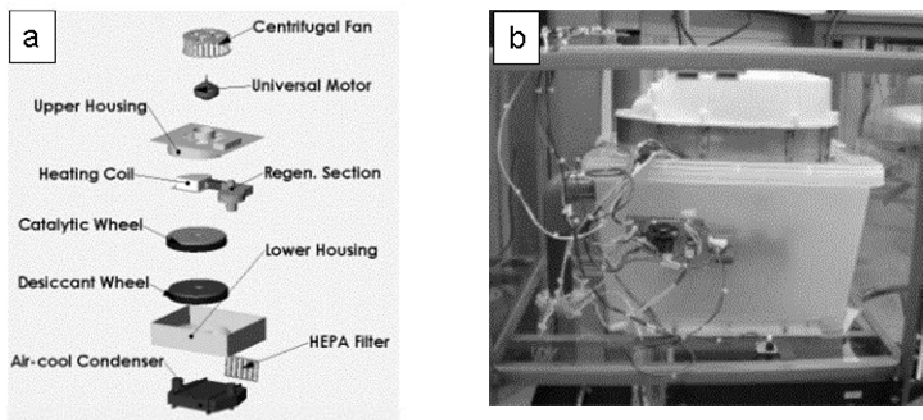


Figure 12.8-9. (a) schematic drawing of component parts and their arrangement in the prototype unit design 1 and (b) a picture of the assembled prototype.

Sensors were inserted in the prototype to monitor the temperature (National Semiconductors, LM35-DZ), humidity (Honeywell, HIH-3605-B) and total VOC concentration (FIS, SP3-AQ2) at various locations shown in Fig. 12.8-10. The data were collected by a data logger (Picolog, ADC-16) and analyzed. The temperature profiles from the preliminary test showed that poor seal between the hot and cool air streams compromised the prototype performance. Hot spots and uncontrollable temperature rise prevented further tests. This clearly showed that the complicated design is not suitable.

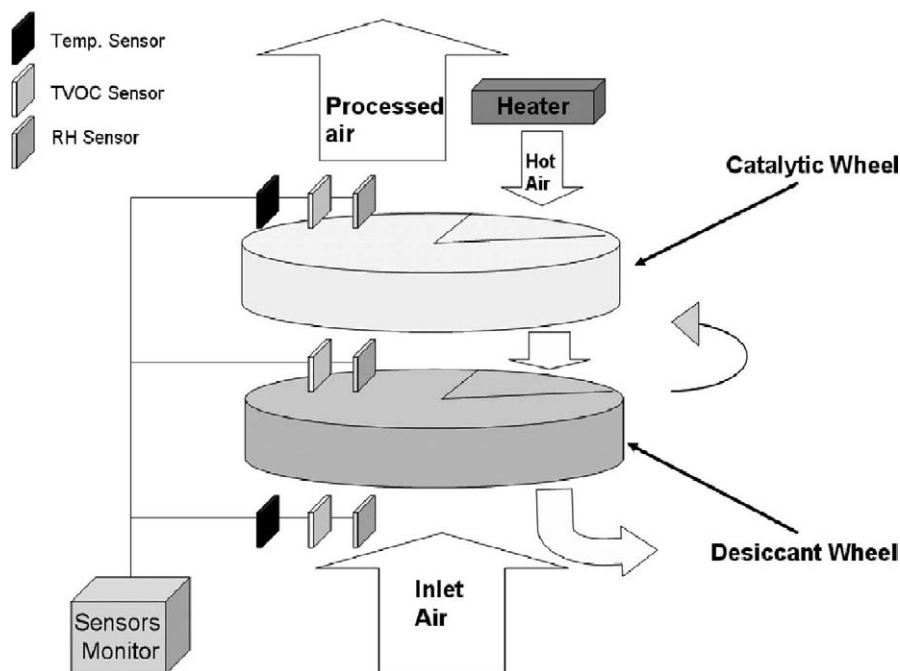


Figure 12.8-10. Schematic drawing of the prototype unit design 1 showing the locations of the temperature, humidity and total VOC sensors.

12.8.9 Prototype Unit Design 3

The prototype design 2 was expected to have similar air seal problems as the prototype 1 therefore the prototype design 3 was constructed and tested, instead. Since all the modification was restricted to the wheel, prototype design 3 allowed us to simply use the existing commercial appliance design. The dehumidifier was first test run under different operating conditions and the airflow, temperature and humidity at different locations within the appliance were measured and recorded. The airflow, temperature and humidity profiles were used to calculate the optimum quantities and distributions of catalysts and adsorbents in the wheel (Fig. 12.8-6). The wheel was replaced in the dehumidifier appliance and tested with sensors inserted at the locations shown in Fig. 12.8-11. The results show that the airflows and temperatures remained within normal operating values. Laboratory and field tests were conducted and the results are reported in the next section.

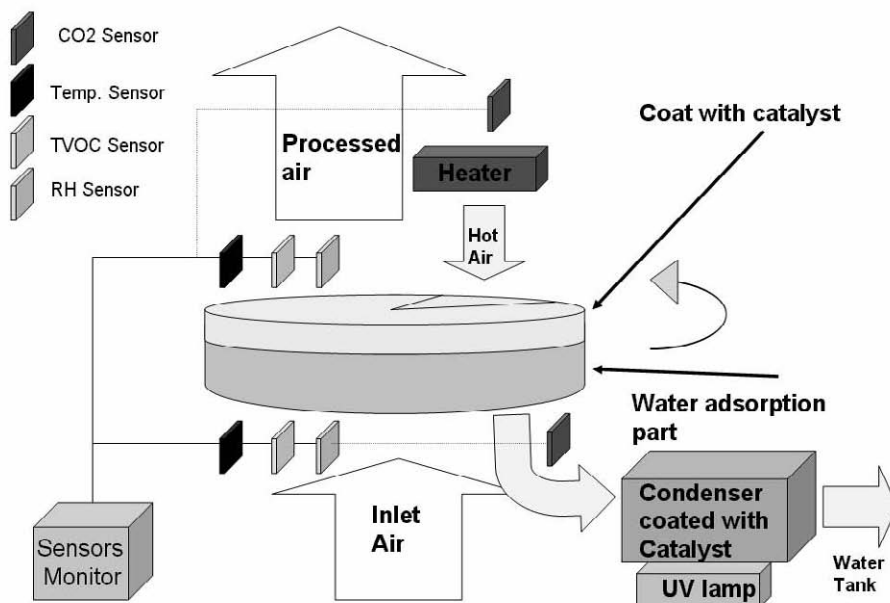


Figure 12.8-11. Schematic drawing of the prototype unit design 3 showing the locations of the temperature, humidity and total VOC sensors.

12.9 LABORATORY AND FIELD TESTS

Phase two of the project commenced in May 2003 with the objectives of implementing the new catalyst formulation and prototype design and conducting detailed performance tests in the laboratory and field sites. The single catalyst/adsorbent/desiccant wheel has the advantage of simpler design and lower cost. The new prototype design was implemented towards the end of the spring semester and a new team of undergraduate students was recruited to continue the project. Ms. Hazel Lai Wing Yan, Ms. Vivian Chan Ngar Wai, Mr. Kenneth Leung Wai Kin and Mr. Owen Luk Ka Fai were all first year Chemical Engineering students. Mr. Anthony Ng Ka Hang, a graduate of Manufacturing and Industrial Engineering and former employee of Honeywell Consumer Products (HK) Ltd. joined to lead the team of undergraduates and take charge of prototype fabrication and testing. Hazel and Vivian were responsible for the laboratory tests, while Kenneth and Owen carried out the field tests. The FYP students remained for a month to help in the new prototype design and in

training the new team. Mr. Victor Lo of Global Manufacturing Services Ltd. and Mr. Eddy Wu of Chiaphua Industries Ltd. remained the project's main industrial partners and consultants.

Eight desiccant-based dehumidifiers (RV-DA60-HC) made by the Japanese company Zojirushi (Fig. 12.9-1a) were purchased with the help of Chiaphua Industries Ltd. The appliance was designed for dehumidification of a 60 m² room at rate of 3.36 L/day when the relative humidity (R.H.) is 50 %. Its airflow can adjusted between 65 and 85 m³/h (i.e., 40 to 50 scfm). The normal outlet air temperature is 35 °C, but can reach temperatures up to 56 °C at high-speed setting. Measuring 48 cm in height and 27 cm in width and breadth, the dehumidifier weighs only 6.5 Kg. The main components are air blower, desiccant wheel and motor, air heater, air-cooled condenser, water basin, power supply and a processor-based control unit. The operating parameters including heater temperature, heating rate, desiccant wheel rotation and air blower speed were pre-programmed and cannot be changed without triggering the safety routine that disables the appliance. Twelve grams of formulated catalyst was wash-coated on the desiccant wheel of the dehumidifier (Fig. 12.9-1b) to impart air purification function. The modified dehumidifier will be henceforth referred to as the Prototype Unit.

The performance tests conducted in the laboratory included comparison of airflow, noise and dehumidification data between the Prototype Unit and the original dehumidifier appliance. Test methodologies were designed with reference to the standard test procedures in ANSI/AHAM Standard AC-1-1988 published by the Association of Home Appliance Manufacturers (AHAM), but adapted to the available equipment. In addition, the reductions of VOC and bioaerosols by the Prototype Unit were measured by a new dynamic test method. It enabled the collection of real time performance data and direct monitoring of the appliance operation. The undergraduate students must obtain permission for field test from the University as well as the catering manager of the HKUST University canteen, the doctor of the public government clinic for elderly and the manager of the Home of Loving Faithfulness. Figure 12.9-2 shows the timeline of the phase two of the project.

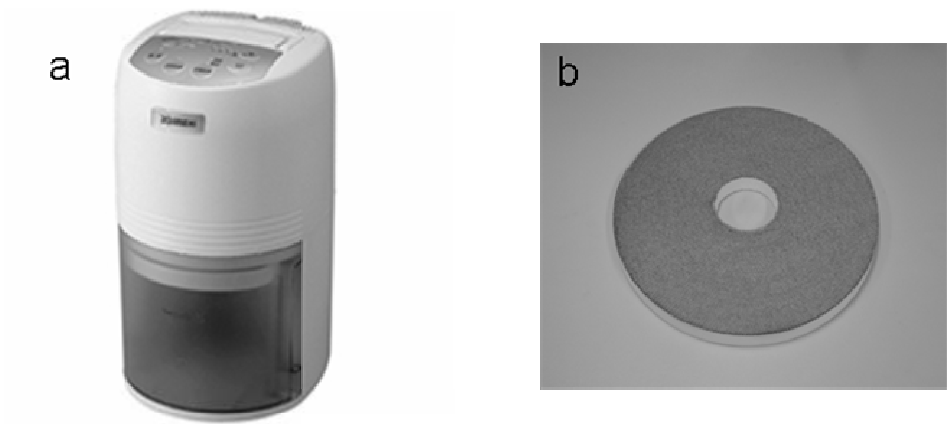


Figure 12.9-1. Pictures of (a) dessicant-based dehumidifier and (b) dessicant wheel.

Description for the Laboratory and Field Tests of Prototype Unit	2003												2004																													
	May 5/1	May 6/1	Jun 6/1	Jul 7/1	Jul 7/15	Aug 8/1	Aug 8/15	Sep 9/1	Sep 9/15	Oct 10/1	Oct 10/15	Nov 11/1	Nov 11/15	Dec 12/1	Dec 12/15	Jan 1/1	Jan 1/15	Feb 2/1	Feb 2/15	Mar 3/1	Mar 3/15	Apr 4/1	Apr 4/15	May 5/1	May 5/15	Jun 6/1	Jun 6/15	Jul 7/1	Jul 7/15	Aug 8/1	Aug 8/15	Sep 9/1	Sep 9/15	Oct 10/1	Oct 10/15	Nov 11/1	Nov 11/15	Dec 12/1	Dec 12/15			
Laboratory Test (Study the performance of airflow, noise, dehumidification, VOC remediation and bioaerosol remediation for the prototype.)																																										
a. Airflow and Noise Measurement																																										
b. Dehumidification Test																																										
c. VOC Removal and Remediation [1]																																										
d. Bioaerosol Removal & Remediation [2] [3]																																										
Field Test (Study the removal efficiencies of formaldehyde, carbon monoxide, odorous compounds and biological aerosols in indoor environment.)																																										
a. UST University Canteen [4]																																										
b. AMI Conference Room, HKUST																																										
c. Public Clinic for Elderly [5]																																										
d. Charity Home for Handicapped Children [6]																																										

Remarks:

[1] Prototype unit was evaluated, as a flow reactor by adding a ductworks to the air inlet and outlet, and conducted in a fume cupboard at ambient temperature and humidity.

[2] Germicidal properties tests were conducted, for *B. subtilis*, *P. aeruginosa* and *S. epidermidis*, by distilled water (positive control), bleach solution (negative control), 75% alcohol and c

[3] Bioaerosol tests were conducted, on the Prototype Unit for *B. subtilis*, *P. aeruginosa* and *S. epidermidis*, in a Class II Biological Safety Cabinet at the Applied Technology Center, HKUST.

[4] Tests were conducted for the reduction of natural bioaerosol at the University canteen during the peak lunch hours, daily for one month..

[5] On-site test is one of the busiest commercial areas in HK and the roadside air pollution index for much the year is "High".

[6] On-site test is situated between two busy highways and next to a Tofu factory. Thus, the particulate and bioaerosol levels at the site were "High".

Figure 12.9-2. Project timeline for phase 2.

A. Laboratory Performance Data

Laboratory tests were conducted for airflow, noise, dehumidification and VOC remediation by the prototype.

12.9.1 Airflow and Noise Measurements

Airflow measurements were conducted to map the airflow distribution along the inlet and outlet of the prototype. This is essential for positioning of the sensor probes for transient monitoring of the temperature, humidity and VOC level at the prototype inlet and outlet. The students conducted the measurements at the laboratory of the Mechanical Engineering Department, HKUST after proper equipment training. The inlet and outlet airflow velocities were measured using VelociCalc Plus Multi-Parameter Ventilation Meter (Model 8386-M-GB) from TSI Inc. for blower speed settings of “normal-speed” equivalent to airflow of 1.33 m³/min (i.e., 48 scfm). The multi-point measurements along the air inlet and outlet (Fig.12.9-3) were obtained and tabulated in Table 12.9-1. It is clear from the results that uniform flow profiles were obtained at both inlet and outlet. This means that the sensor probe located at the central region of the inlet and outlet will give representative measure of the airstream conditions.

The noise level was also measured using Interacting Sound Level Meter (NL04) from RION for blower speed setting of “normal-speed” near the inlet and outlet of the Prototype Unit. The average noise levels are 23 and 48 dB at the inlet and outlet, respectively. These values are low compared to most air dehumidifier and air purifier appliances.

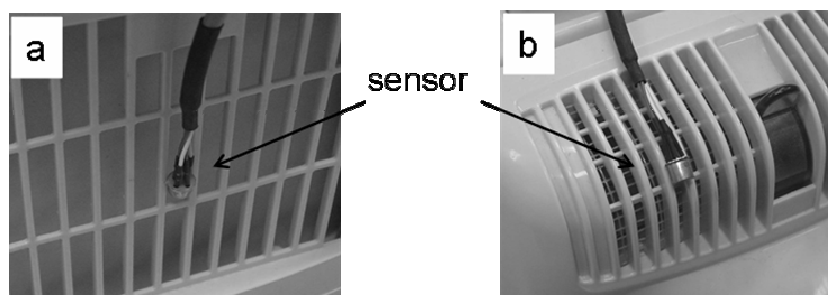


Figure 12.9-3. Airflow measurement points along (a) inlet and (b) outlet areas of the Prototype Unit.

Table 12.9-1. Inlet and outlet airflows at a blower setting of normal-speed

Inlet Air Velocity (m/s)							Outlet Air Velocity (m/s)			
Position	A	B	C	D	E	F	Position	A	B	C
1	1.07	1.11	1.03	1.04	1.12	1.01	1	5.31	5.42	5.29
2	1.06	1.10	0.98	1.05	1.12	1.03	2	5.27	5.47	5.33
3	1.04	1.10	1.01	1.02	1.11	1.04	3	5.37	5.41	5.36

12.9.2 Dehumidification Test

The dehumidification rate for the Prototype Unit was measured and compared with an unmodified dehumidifier. The Prototype Unit and dehumidifier appliance were placed in a 60 m² room with open windows. The test was conducted at an ambient temperature of 23 °C and relative humidity of 80 %. The amount of water collected after 8 h was weighed and dehumidification rates of 0.14 Kg/h and 0.13 Kg/h were obtained for the Prototype Unit and unmodified dehumidifier, respectively. This indicates that coating the formulated catalysts onto the desiccant wheel does not significantly affect its dehumidification function.

12.9.3 VOC Removal and Remediation

Environmental test chambers are expensive and were not available for the tests needed in the project. It was decided that the Prototype Unit would be evaluated as a flow reactor. Ductworks were added to the air inlet and outlet to ensure uniform airflow and to prevent inadvertent mixing of the two airstreams. Figure 12.9-4 shows a schematic drawing of the experimental setup. The tests were conducted in a fume cupboard at ambient temperature (20-30°C) and humidity (60-80 % RH). The VOC was evaporated and mixed with air before entering the inlet of the Prototype Unit. The inlet and outlet conditions were monitored in real time. The sensors used for the tests are VOC gas sensor Model Type D1 (# TGS 2602) from FIGARO, humidity sensor Model Ceramic SIL (HIH-3605-A) from Honeywell and temperature sensor Model DZ Version (LM35 DZ) from National Semiconductor. The sensor box was designed and built by with collaboration with an Electronic Engineering student at HKUST. The VOC sensors were calibrated against Photoionization Gas Detector Model PGM-30 from RAE using the target VOC. The humidity and temperature sensors were calibrated using VelociCalc Plus Multi-Parameter Ventilation Model (8386-M-GB) from TSI Inc. A set of VOC, humidity and temperature sensors was placed at the inlet and outlet of the Prototype Unit. A Digital Multi-Gas Monitor (1302) from Bruel & Kjaer recorded the outlet carbon dioxide level. Continuous monitoring of VOC removal, temperature and humidity fluctuations and CO₂ generation were conducted with each experiment lasting 8 h. The data were collected at 1-second interval by a personal computer using PICO software.

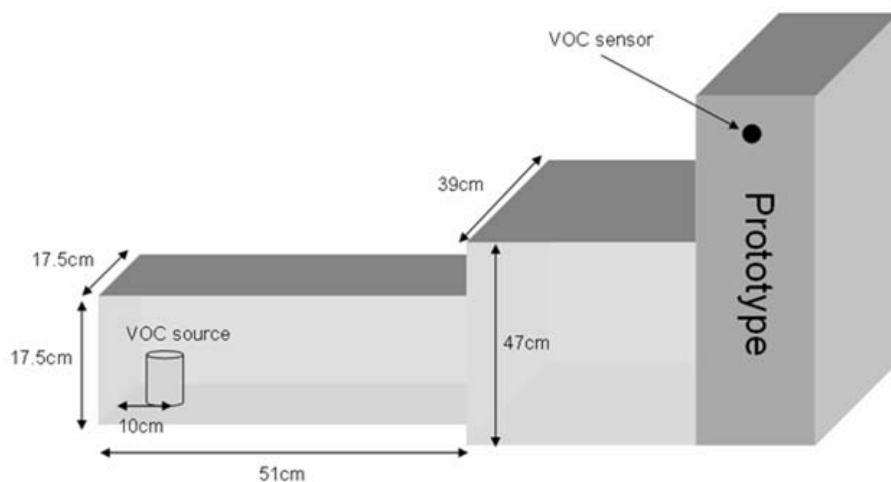


Figure 12.9-4. Schematic diagram VOC experimental test setup.

The results of a four hours experiment are shown in Fig. 12.9-5 as an illustration. About 15 ppm of ethanol was evaporated and mixed with air drawn in from the surrounding. Figures 12.9-5a & 12.9-5b show that the inlet air temperature and relative humidity are constant at 23 °C and 76 %. The inlet VOC level shown in Fig. 31c fluctuates between 12-20 ppm as the VOC liquid level changes during evaporation. The outlet conditions were monitored in real time and are shown in the figures. The outlet air temperature was 55 °C and the relative humidity was 25 %. This is consistent with the normal operation of unmodified dehumidifier unit. The average outlet VOC level was 3 ppm and an average 75 % VOC removal per pass was obtained, which is equivalent to a removal rate of 42 mmole/h of ethanol. The carbon dioxide level increases from the ambient level of 300 ppm to 400 ppm at the outlet giving an average CO₂ production rate of 110 mmole/h, indicating a complete oxidation of ethanol to carbon dioxide and water. The amount of carbon dioxide detected at the outlet was higher than expected from the carbon balance and may be due to the oxidation of airborne microorganisms and organic aerosols present in ambient air.

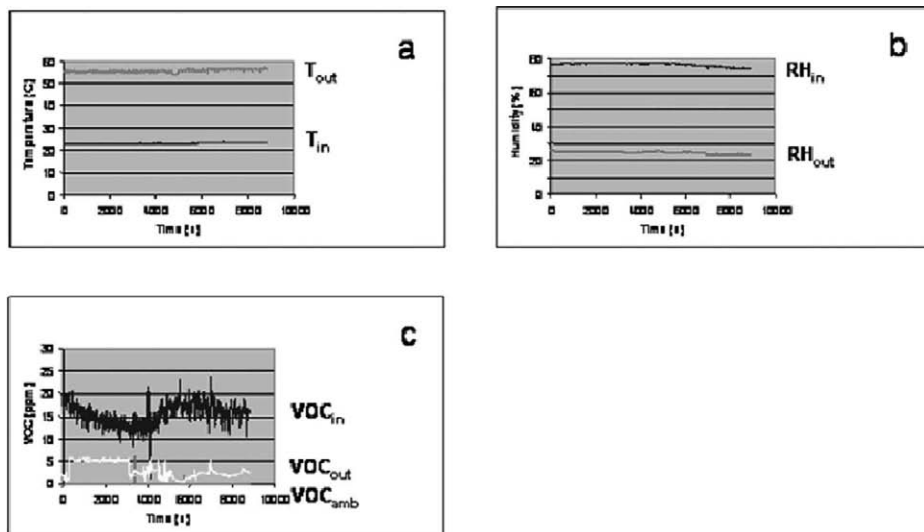


Figure 12.9-5. Plots of (a) air temperature, (b) relative humidity and (c) airborne VOC at the inlet and outlet of the Prototype Unit.

Table 12.9-3 summarizes the results of the VOC removal and remediation tests conducted on the Prototype Unit. The results indicate that better than 75 % per pass reduction can be obtained for VOC level less than 50 ppm. At least 50 % reduction is obtained for concentrated VOC (> 50 ppm) airstream. The conversion rate depends on the VOC and its concentration. The Prototype Unit is very effective in removing odorous compounds such as Chinese incense and air freshener used in most Hong Kong household.

A small 3 cm x 3.5 cm section of the catalyst-coated desiccant wheel (25 cm diameter) was cut and placed in specially made holder shown in Fig. 12.9-6a. The piece of sample was tested in a 0.2 m³ environmental chamber at Chiaphua Industries Ltd. (Fig. 12.9-6b) for reduction of airborne VOC. The chamber was filled with the target VOCs through two stage saturators shown in Fig. 32b. Once the VOC level in the chamber stabilized, the fan was turned on to circulate the air through the sample. Three sets of sensors were located at the inlet and outlet of the holder, as well as in the center of the chamber. The chamber temperature and relative humidity were kept constant during the test. Figure 12.9-6c shows the results for VOC levels of 4000, 2000 and 1000 ppb at room temperature. The reduction rate was slower because of the low VOC concentration and the poor air circulation in the chamber. Also unlike the Prototype Unit, the catalyst was kept at room temperature throughout the test.

Nevertheless, fifty percent VOC reductions were achieved in the first fifteen minutes of the test.

Table 12.9-3. Prototype Unit field test performance for different volatile organic compounds

Test VOC	Concentration (ppm)	Percent removal per pass	Removal rate (mg/h)
Ethanol	20	75	30
	30	85	50
	100	80	150
Acetone	150	60	180
Benzene	150	60	180
Toluene	100	60	120
Ethylbenzene	100	95	180
Thinner	400	50	380
Chinese Incense	20	100	40
Air Freshener	20	100	40

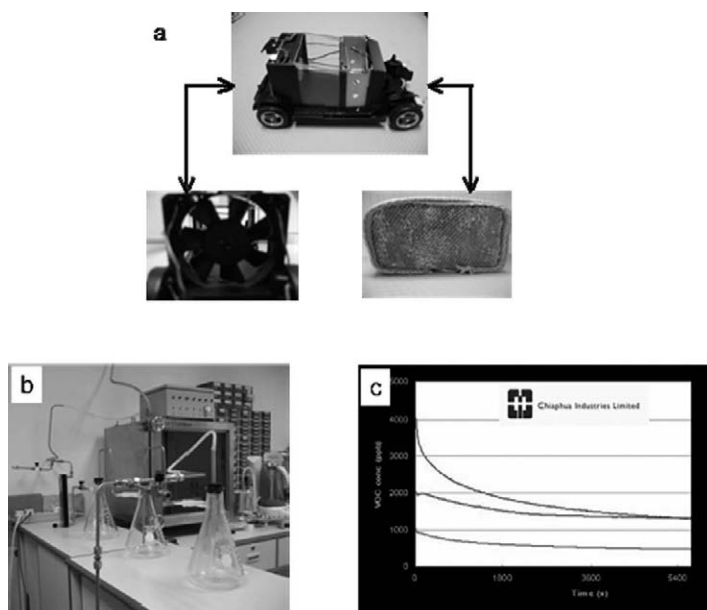


Figure 12.9-6. A small prototype unit (a) consists of a fan and coated monolith was placed in a test chamber shown in (b) and tested for VOC removal at ambient conditions. (c) The results show that the VOC level was decreased by half in less than an hour.

12.9.4 Bioaerosol Removal and Remediation

The germicidal properties of the nanostructured TiO_2 catalyst support was tested for *Bacillus subtilis*, *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*. Circular pieces of filter papers (5 mm diameter) were saturated with distilled water (positive control); bleach solution (negative control), 75 % alcohol and different concentration of TiO_2 . The TiO_2 has similar germicidal effectiveness as 75 % alcohol as shown in Fig. 12.9-7. This shows that the TiO_2 catalyst support exhibits intrinsic germicidal properties.

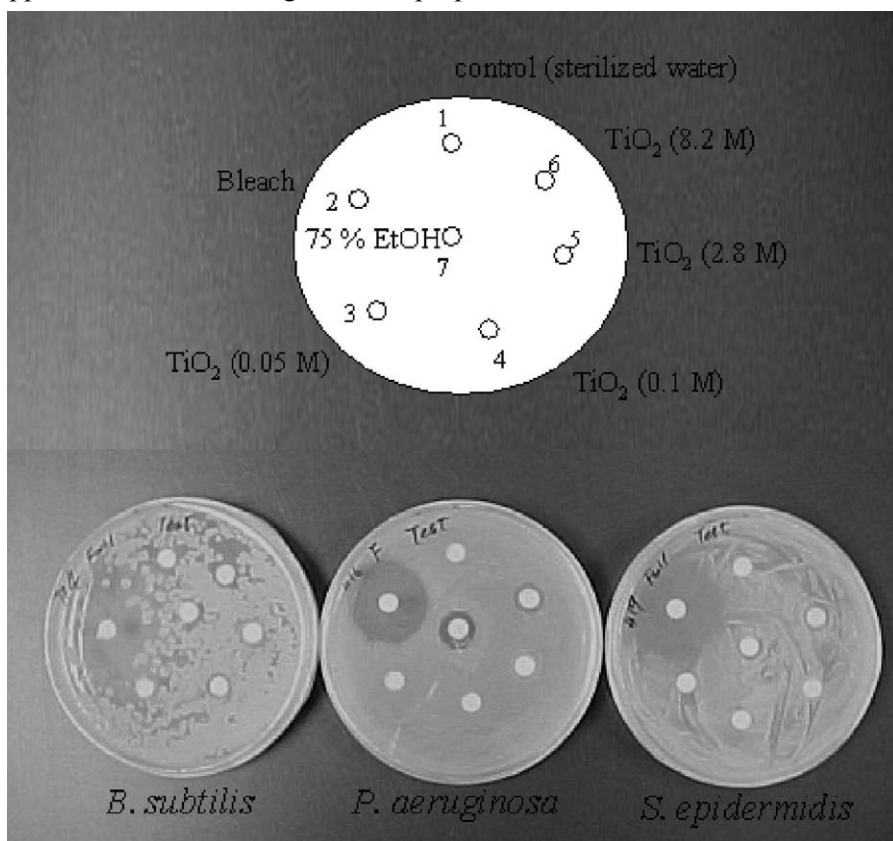


Figure 12.9-7. Pictures of germicidal test for nanostructured TiO_2 for *B. subtilis*, *P. aeruginosa* and *S. epidermidis*.

The intrinsic germicidal property of the TiO_2 support was also tested for natural indoor bioaerosol. A piece of cotton cloth was coated with a colloidal suspension of the nanostructured TiO_2 . After drying, a circular piece of the cloth was cut and fitted inside the Andersen viable single-stage sampler in such a way

that air flows through the cloth before impacting on the collection plate. Tryptic soy agar (TSA) and malt extract agar (MEA) plates were respectively used for bacteria and fungi samplings. Two additional Andersen viable single-stage samplers were used to measure the ambient bioaerosol level and the amount of bioaerosol filtered by the cloth. The three samplers were operated at the same time and air samples were collected at 28.3 L/min for five minutes. The total bioaerosol level varied between 200 to 800 CFU/m³ during the test. Figure 34 shows that the cotton cloth filtered roughly ten percent of the airborne bacteria and fifteen percent of the airborne fungi. These values remained unchanged during the 1 h experiment. TiO₂ deactivates and kills microorganisms by direct contact. Nearly sixty percent reduction of airborne bacteria (Fig. 12.9-8a) was obtained from the TiO₂-coated cloth at the start of the test. This gradually decreases with time as the TiO₂ was slowly covered with dead microorganisms. Similarly, the forty percent reduction in fungi decreased to thirty percent at the end of the experiment (Fig. 12.9-8b).

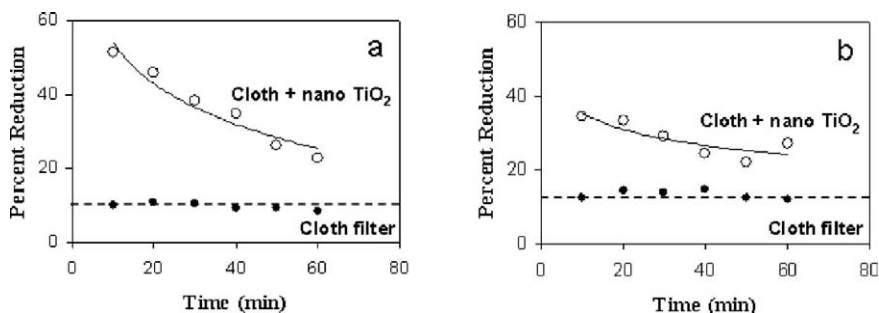


Figure 12.9-8. Plots of (a) percent bacterial reduction and (b) percent fungi reduction as a function of time for uncoated and TiO₂-coated, cotton clothes.

Other components of the formulated catalyst were also tested for their germicidal properties. The desiccant is a good bactericide and cloth coated with the desiccant maintained a sixty percent reduction during the entire test as shown in Fig. 12.9-9a. The desiccant deactivates and kills the bacteria by rapid dehydration. However, this process is not as effective for airborne fungi (Fig. 12.9-9b).

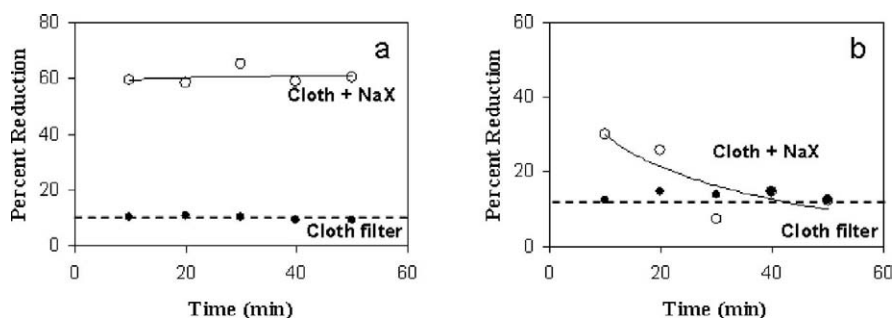


Figure 12.9-9. Plots of (a) percent bacterial reduction and (b) percent fungi reduction as a function of time for uncoated and desiccant-coated, cotton clothes.

Bioaerosol tests on the Prototype Unit were conducted for *B. subtilis*, *P. aeruginosa* and *S. epidermidis*. These are common airborne bacteria found in Hong Kong. The tests were conducted in a Class II Biological Safety Cabinet at the Applied Technology Center, HKUST. The cabinet was sealed with a plastic curtain and the blower was turned off during the test. Two fifteen millilitres of sterilized distilled water were aerosolised with a nebuliser to adjust the relative humidity inside the cabinet to 80 % in order to minimize the evaporative effect on the aerosolised bacteria. The cabinet was kept at room temperature (i.e., 23–24°C) for the test. Ten millilitres stock bacteria culture solution (10^7 to 10^8 bacteria per ml) were aerosolised and uniformly dispersed inside the cabinet. Tests were conducted with the Prototype Unit turned on and off (i.e., control test). It is important to note that filter was not installed in the prototype during tests. Air samples were collected at various times using an Andersen viable single-stage sampler placed 60 cm from the Prototype Unit during the ten minutes test run and duplicate tests were carried out to establish reproducibility. The bacteria plates were incubated in a standard incubator at 37°C for 18 h. The bacterial colonies on each plate were counted as total colony forming unit (CFU).

The test results in Fig. 12.9-10 show a clear and immediate reduction in airborne bacteria when the Prototype Unit was turned on. Ninety percent reduction of *B. subtilis*, *P. aeruginosa* and *S. epidermidis* were reached at 1.5, 10 and 3 minutes of Prototype operation, respectively. The control experiments showed fluctuations due to poor circulation within the test chamber, but otherwise maintained a bacteria level higher than when the Prototype Unit was in operation.

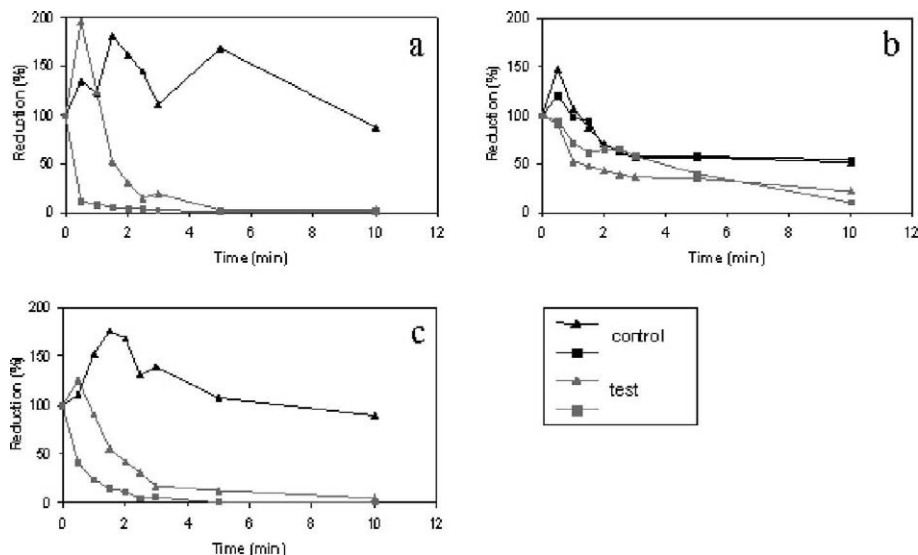


Figure 12.9-10. Plots of airborne bacteria reduction as a function of time for (a) *B. subtilis*, (b) *P. aeruginosa* and (c) *S. epidermidis*.

After the experiments, the Prototype Unit was disassembled and the component parts were individually swabbed with sterilized cotton wools (4 cm^2). Each samples were stored in 1 ml sterilized distilled water in an eppendorf tube. $50 \mu\text{l}$ of sample was transferred to TSA and MEA plates. The TSA plates were incubated at 37°C for 24 h and bacterial colonies were counted. The number of fungal colonies was determined from the MEA plates after incubating at 30°C for 5 days. The results show no viable bacterial and fungal colonies were present in the interior parts of the Prototype Unit. Viable colonies are found on the external surface of the unit. This suggests that air passing through the Prototype Unit was sterilized by the action of the formulated catalyst.

B. Field Performance Data

School canteens and public eateries where large number of peoples congregates often have poor air quality (cf. Table 12.6-6). Air quality survey of Hong Kong restaurants reported high VOC and bioaerosol levels. Also, strong odor from cooking is one of the main complaints. The HKUST canteen was selected as one of the sites for testing. The elderly and the young are vulnerable to the effects of poor air quality. Permission was obtained to conduct field test at a Hong Kong government public clinic for the elderly and at a charitable home for handicapped children. It is important to note that filter was not installed in the prototypes for these tests.

12.9.5 HKUST University Canteen

The bioaerosol removal by the Prototype Unit was tested for the reduction of natural bioaerosol (i.e., bacteria and fungi) at the HKUST University canteen during the peak lunch hours, daily for one month. The site has an average bioaerosol loading of 800 CFU/m³, but values as high as 1200 CFU/m³ are not unusual. About 90 % of the bioaerosols are bacteria and 10 % are fungi. Sixty percent of the bacteria are gram negative with close to forty percent having an average size between 1-2 microns. Only 10 % of the bacteria have size smaller than 1 micron and the remaining 50 % are larger than 2 microns. The common bacterial and fungi species are *Micrococcus*, *Staphylococcus epidermis*, *Cladosporium*, *Penicillium* and *Yeast*. Pictures of the canteen and the location of the Prototype Unit are shown in Figure 12.9-11.



Figure 12.9-11. Pictures of the University canteen during the peak lunch hour. The location of test is shown by the red spot in Fig. 12.9-11c.

A pair of Andersen viable single-stage samplers was located at the Prototype Unit's inlet and exit to measure the reduction of bioaerosol. Sampling was done simultaneously at a sampling rate of 28.3 L/min for 5 minutes. TSA and MEA plates were used for sampling bacteria and fungi, respectively. Six measurements were carried out daily for bacteria and fungi. Typical results for a test run are shown in Table 12.9-4. The Prototype Unit maintained a better than 60 % per pass removal and kill of airborne bacteria at loadings as high as 1200 CFU/m³. The average fungi reduction is 90 % during the one month, field test. These values are comparable to most air cleaners equipped with high efficiency filter, but in this case the microorganisms were also killed.

Biweekly laboratory VOC removal and remediation tests were conducted using 10-15 ppm of ethanol. The VOC removal remained unchanged at around 80 % per pass or 40 mmole/h.

Table 12.9-4. An example of a single day prototype Unit field test results at HKUST University canteen.

	Measurement	In (CFU/m ³)	Out (CFU/m ³)	% Reduction per pass
Bacteria	1	1290	540	58
	2	860	300	65
	3	950	280	71
	4	1100	470	57
	5	780	370	53
	6	900	420	54
	Average			60 ± 7
Fungi	1	110	10	91
	2	140	40	71
	3	180	10	95
	4	120	30	75
	5	150	40	73
	6	150	20	87
	Average			82 ± 10

12.9.6 Public Clinic for the Elderly

Permission was obtained to conduct an on-site test of the Prototype Unit at a Wan Chai Public Clinic for the Elderly located at the second floor of Southorn Centre at Wan Chai, Hong Kong. The location is one of the busiest commercial areas in Hong Kong and the roadside air pollution index (API) for much the year is "High". The clinic occupied an area of 36 m² (Fig. 12.9-12a) and consisted of the doctor's consultation room (12 m²), a private interview room (6

m²) and an open space for the reception area and nurse station (18 m²). The clinic saw forty to sixty elderly patients everyday and was staffed by one doctor and four clerks and nurses. At any one time, there are on average 10 patients and 3 staffs at the reception area and 3 persons in the doctor's consultation room.

The field test was conducted from May 2003, towards the end of the Severe Acute Respiratory Syndrome (SARS) outbreak in Hong Kong, until January 2004. The students taking part in the field tests were properly trained and equipped with medical safety equipment. Air samples collected at the reception area was designated as control samples (Fig. 12.9-12b). The Prototype Unit was located in the doctor's consultation room (Fig. 12.9-12c) and was operated 10 h/day, 6 days/week during the six months test period.

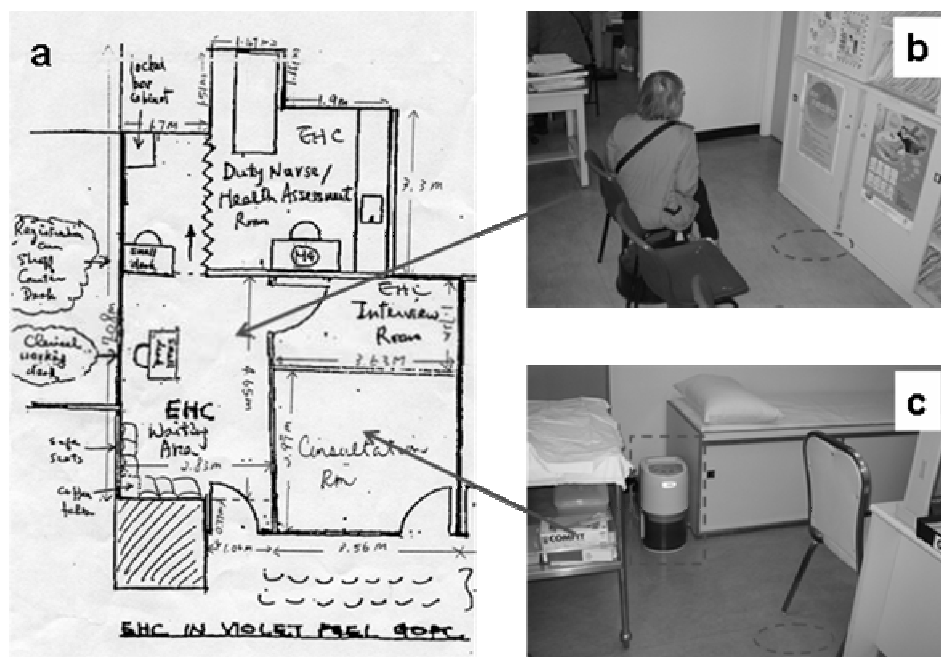


Figure 12.9-12 (a) A drawing of the clinic floor plan, (b) picture of the reception area where control air samples were taken and (c) picture of the doctor's clinic room where field testing of the Prototype Unit was conducted.

Five weeks air survey was conducted to determine the air quality at the clinic. The reception area has a lower bioaerosol loading of 300-800 CFU/m³ owing to better airflow and open floor plan. The doctor's consultation room displays 2-to-3 times higher amount of airborne bioaerosol (i.e., 600-1400 CFU/m³) due to poor air ventilation. The airflow is roughly 0.1 m³/s, giving an overall air

exchange rate of about 1-2 per hour. The bioaerosol level at the reception area fluctuates from over 800 CFU/m³ during the opening hours in the morning and afternoon when most of the patients arrived for consultation to lows of 300 CFU/m³ during lunch break and closing time. Analysis of air sample identified eight bacterial species and seven fungal and yeast species. Micrococcus and Staphylococcus accounted for 85 % of the airborne bacteria in the clinic. The remaining 15 % belongs to the other five unidentified bacterial strains isolated from the survey. Further analysis was not conducted for fear that they may belong to virulent pathogens. Cladosporium, Pennicillium, Emmonsia and Yeast were detected in the clinic air. These bacteria and fungi are commonly found in Hong Kong.

Tables 12.9-5 and 12.9-6 summarize the results of the three months period when weekly measurements were conducted. The temperature and humidity of the clinic is relative constant at around 23 °C and 80 %, but the bioaerosol level changes by the hour and day-to-day depending on the number of patients and outside air quality. The Prototype Unit was placed in the doctor's consultation room and the airflow was set at normal-speed (Fig. 12.9-12c), allowing a complete exchange of the room's air every 30 minutes. The air sample from the reception and doctor's consultation room were sampled within 20 minutes of each other. The data in the tables show that the airborne microorganisms in the doctor's consultation room remained higher compared to the reception area. However, this is a significant improvement when compared to the level when the Prototype Unit was not in use. Data obtained by measuring the inlet and outlet bioaerosol in the Prototype Unit indicated that 60 % and 67 % reduction in airborne bacteria and fungi was obtained, respectively. The performance was maintained during the six months test.

The doctor, nurses and clinic staffs reported a noticeable improvement of air quality in the doctor's consultation room with the disappearance of odors associated with patients and disinfectants. There were also significant drop in doctor absenteeism due to flu and respiratory illnesses during the six months.

After the six-month field test, the Prototype Unit was disassembled and the component parts were individually swabbed with sterilized cotton wools (4 cm²). Each samples were stored in 1 ml sterilized distilled water and 50 µl of samples were transferred to TSA and MEA plates. The TSA plates were incubated at 37 °C for 24 h and bacterial colonies were counted. The number of fungal colonies was determined from the MEA plates after incubating at 30 °C for 5 days. The results of the test are shown in Table 12.9-7. The results show that bacteria and fungi thrived near the air intake where they deposited on the grills, panel and around the intake slots. However once the microorganisms are drawn through the catalyst-coated desiccant wheel, the number of viable

microorganisms decreases to zero. This further confirmed that the Prototype Unit is effective in removing and killing airborne microorganisms.

<i>Date (2003)</i>	<i>Reception (CFU/m³)</i>	<i>Consultation Room (CFU/m³)</i>		<i>Prototype Test (CFU/m³)</i>		<i>% Reduction per pass</i>
		before	after	inlet	outlet	
OCT 13	550	1200	600	540	240	56
OCT 22	360	300	250	210	80	62
OCT 27	800	800	450	800	350	56
OCT 29	380	470	250	470	170	64
NOV 05	510	500	420	500	230	54
NOV 08	500	500	200	470	190	60
NOV 10	740	780	630	780	270	65
NOV 12	500	880	690	800	300	63
NOV 19	-	600	510	610	280	54
NOV 26	650	720	610	690	250	64
DEC 03	370	690	510	430	180	58
DEC 10	420	710	420	420	170	60
Average						60

Table 12.9-5. Prototype Unit performance for reduction of airborne bacteria.

Table 12.9-6. Prototype Unit performance for reduction of airborne fungi.

<i>Date (2003)</i>	<i>Reception (CFU/m³)</i>	<i>Consultation Room (CFU/m³)</i>		<i>Prototype Test (CFU/m³)</i>		<i>% Reduction per pass</i>
		before	after	inlet	outlet	
OCT 13	85	110	56	110	35	68
OCT 22	40	56	35	56	14	75
OCT 27	28	20	14	28	7	75
OCT 29	21	21	7	21	7	66
NOV 05	21	21	14	14	7	50
NOV 08	35	50	28	70	21	70
NOV 10	56	78	56	70	28	60
NOV 12	63	70	28	63	28	56
NOV 19	50	91	35	91	35	62
NOV 26	42	57	35	57	28	51
DEC 03	42	35	28	28	7	75
DEC 10	35	63	42	35	7	80
Average						67

Part No.	Part Description	Total Bacteria Count (CFU/m ³)		Total Fungal Count (CFU/m ³)	
		external	internal	external	internal
1	Blank Control 1	0	N.A.	0	N.A.
2	Blank Control 2	0	N.A.	0	N.A.
3	External Casing	40	N.A.	0	N.A.
4	Intake Grill	120	20	40	0
5	Intake Panel	1300	N.A.	20	0
6	Intake Air slot 1	40	N.A.	0	N.A.
7	Intake Air Slot 2	20	N.A.	60	N.A.
8	Dessicant Wheel (inlet side) Q1	220	N.A.	0	N.A.
9	Dessicant Wheel (inlet side) Q2	40	N.A.	0	N.A.
10	Dessicant Wheel (inlet side) Q3	0	N.A.	0	N.A.
11	Dessicant Wheel (inlet side) Q4	0	N.A.	0	N.A.
12	Dessicant Wheel (outlet side) Q1	0	N.A.	0	N.A.
13	Dessicant Wheel (outlet side) Q2	0	N.A.	0	N.A.
14	Dessicant Wheel (outlet side) Q3	0	N.A.	10	N.A.
15	Dessicant Wheel (outlet side) Q4	0	N.A.	0	N.A.
16	Blower Fan Blade	0	0	0	0
17	Air Outlet 1	0	0	0	0
18	Air Outlet 2	0	0	0	0

Table 12.9-7. Viable bacteria and fungi found on the Prototype Unit

The Prototype Unit was cleaned and tested for VOC removal and remediation using 10-15 ppm of ethanol. The VOC removal remained unchanged at around 80 % per pass or 40 mmole/h. This indicates that the formulated catalyst remained active after a total of one-month laboratory test and six months of field study at the clinic. The Prototype Unit was given as a gift to the doctor for permitting us to conduct the field test at the clinic.

12.9.7 Charity Home for Handicapped Children

Four prototypes were built and tested during the months of September and October 2003. The new prototypes were tested and the performances for VOC and bioaerosol removal and remediation were within 90 % of the benchmark unit (cf. Table 12.9-3 & Fig. 12.9-10). Permission was obtained to field test two

of the Prototype Units at the Home of the Loving Faithfulness at Castle Peak Road, Sheung Shui. The Home is situated between two busy highways and next to a Tofu factory. Therefore, the particulate and bioaerosol levels at the site were high, and this was believed to be the main contributing factor in the high incidence of respiratory illnesses in the children. The two Prototype Units were placed at one of the children's room (120 m²) shown in Fig. 12.9-13 and were operated 10 h/day for 7 days a week from May until September of 2004. The room houses ten children and only has one window-mounted, air conditioner that was turned on occasionally during summer nights, but more often windows were left opened and the fan was turned on. This means that the room temperature and humidity fluctuates depending on the weather. The temperature ranges between 22 to 33 °C and the relative humidity was between 60 to 92 % during the three months measurement. Also, the particulate and bioaerosol levels can change dramatically from day to day.



Figure 12.9-13. Pictures of the children's room at the Home of Loving Faithfulness.

Table 12.9-8 summarizes the results of field test conducted at the Home. The measurements were taken on two successive days with the windows open. Air samples taken next to the open window was used as control. Air samples taken at the middle of the room was assumed to represent the conditions of the room. The data shows that Prototype Unit was able to keep the airborne bacteria level in the room reasonable low compared to outside. Also, the Prototype Unit displays on average 52 % reduction per pass which is within the performance specification.

A slight drop in the performance was attributed to fouling due to the high particulate level. This was remedied by simply washing the desiccant wheel and by placing a coarse foam filter at the air intake. The Prototype Units were also disassembled and swabbed to check for viable bacteria and fungi. The result is similar to the previous Prototype Unit used in clinic. The number of viable microorganisms is higher at the air intake and close to zero at the desiccant wheel and air outlet.

Table 12.9-8. Prototype Unit performance for reduction of airborne bacteria.

Date (2004)	Control (CFU/m ³)	Children's Room (CFU/m ³)	% Reduction for Children's Room	Prototype Test (CFU/m ³)		% Reduction per pass
				inlet	outlet	
MAY 05	1100	500	55	500	220	56
MAY 06	-	480	-	630	180	71
MAY 18	950	550	42	470	220	53
MAY 19	1250	500	60	590	180	70
JUN 08	1200	570	53	700	380	46
JUN 09	850	580	32	750	400	47
JUN 15	750	300	60	1050	470	55
JUN 16	1280	930	27	750	420	44
AUG 02	820	572	30	650	290	55
AUG 03	650	570	12	530	290	45
AUG 16	840	500	40	480	310	35
AUG 17	540	420	24	530	280	48
Average						52

12.10 CONCLUDING REMARKS

The project has successfully introduced important elements of entrepreneurship and product design in the final year design project as part of Chemical Engineering student education. The success of project owed a lot to the excellent work of the undergraduate students, the participation of the various postgraduate, faculty, industrial partners and the support from the School of Engineering. The project is in part funded by the Hong Kong Innovation and Technology Commission (ITS/176/01C) to whom the author expresses sincere thanks.

REFERENCE

1. G.W. Wang, Hong Kong History: New Perspectives, San lian shu dian, 1997.
2. Data provided by the Hong Kong Government Census and Statistics Department for the year of 2001.
3. Hong Kong Annual Digest of Statistics
4. S. Turner, *Tools for success*, The McGraw-Hill Companies, London, 2002.
5. M. Gladwell, *Blink: the power of thinking without thinking*, Little Brown and Co., New York, 2005.
6. Data provided by the Hong Kong Government Planning Department.
7. Data provided by the Hong Kong Environmental Protection Department.
8. H.P. Liu and J.C.L. Chan, *Atmospheric Science*, 36 (2002) 591.
9. C.Y.H. Chao, T.C.W. Tung and J. Burnett, *Indoor Built Environ*, 7 (1998) 110.
10. Data provided by the Hong Kong Observatory.
11. Article published in South China Morning Post, July 9, 1999.
12. Article published in Ming Pau, August 24, 2002.
13. W. Fisk and A. Rosenfeld, *Indoor Air*, 7 (1997) 158.
14. Guidance notes for the management of indoor air quality in offices and public places, HKSAR, 1999.
15. W.M. Li, S.C. Lee and L.Y. Chan, *Science of Total Environment*, 273 (2001) 27.
16. S.C. Lee, W.M. Li and C.H. Ao, *Atmospheric Environment*, 36 (2002) 225.
17. A.F. Mills, *Basic Heat and Mass Transfers 2nd ed.*, Prentice Hall, New Jersey, 1999.
18. K.L. Yeung, N. Yao and K.Y. Ho, "Catalytic material and method of production thereof," U.S. Patent Pending (filed July 7, 2004).
19. Cross, N. *Engineering design methods: strategies for product design*, 3rd ed., Wiley, London, 2000.

Chapter 13

Student Projects in Chemical Product Design

Keith K.H. Choy (ed.) with Contributions from the University of Minnesota

*Department of Chemical Engineering
Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong, P.R. China*

13.1. INTRODUCTION

Cussler and Moggridge (2001) proposed a four-step procedure for chemical product design. In this chapter, six case studies prepared by students at the University of Minnesota are highlighted to illustrate this approach. The first step is the identification of customer needs and the translation of the needs into product specifications. The second step is to generate ideas to fill these needs. In the third step, the best ideas are selected for commercial development. Product manufacture is considered in the last step. These examples are intended for stimulating thinking about the issues involved. Hopefully, they will be further explored by other groups to make them more realistic and complete. The project titles and contributors are given below:

Table 13-1. Summary of Six Cases Studies

Project Title	Student Groups
Optical currency substrate for counterfeit prevention	A. Danner, K. Dietz, D. Hanley, B. Johnson
Oxygen impermeable food wrap	T.M. Kojasoy
Controlled drug release	A. Boddington, C. Grant, I. Omaswa, M. Patel
Solid formulation of low melting point active ingredients	C. Da Cuhna, Z. Negus, J. Porter, A. Thawani
UV shield film	K. Grieser, L. Koesler, R. Korpela, R. Ligman
Adhesives for wet metal surfaces	A. Chan, E. Jayawiyanto, D. Joesuf, J. Liono, S. Mohamad

13.2. NEEDS

Chemical product design begins by identifying customer needs. These needs are often vague, qualitative product qualities. Yet particular specifications must be set for manufacturing the product. The background information for the needs of all of these projects is presented below:

PROJECT 1: Optical Currency Substrate for Counterfeit Prevention

Approximately 252 million dollars in counterfeit U.S. currency is recovered each year. While this is a small percentage of the 540 billion U.S. dollars that are assumed to circulate worldwide, there is clearly a need for more sophisticated security features. A possible solution is to use multilayer coextrusion technology to create an optical polymer substrate for U.S. currency.

The use of polymers as a currency substrate has been considered in many nations. Australia already relies solely on polymer for its currency while other nations such as Romania, China, and Northern Ireland have produced commemorative polymer bills. The substrate of Australian currency is Guardianâ, a biaxially oriented polypropylene, produced by Securrency Ltd. This material is not available commercially and has a distinctive feel from other heat withstanding polymers. The distinctive feel of Guardianâ prevents the use of transparencies or other polymers that can be used in color copiers to produce counterfeit. Security features of Australian currency include unprinted transparent windows where the substrate shows through the bill. The bills also incorporate security features such as micro printing, regions of raised printing, symbols that appear when held to light, and serial numbers that fluoresce under UV light. It has been estimated that polymer notes costs twice as much to manufacture but can remain in circulation four times as long as paper bills. Thus, conversion from paper to polymer notes can actually save money because fewer bills must be produced annually to meet demand.

PROJECT 2: Food Wrap

Preservation of food is an important human activity. Since ancient times, people have kept the food away from the microorganism, oxygen and water, by heating, cooling, sweetening, salting, pickling and so forth. Nowadays, refrigerator, vacuum container, sterilization, food wrap, and chemical preservatives are also used. Our company would like to enter this market. The needs for product preservation are summarized below:

1. The food is still edible after storage.
2. The fruits and vegetables should still be fresh.

3. Prevent growth of aerobic pathogens and spoilage organisms, including molds, on food.
4. No toxic substances would be created during the preservation period of food.
5. Significantly improve keeping qualities of polyunsaturated fats and oils.
6. Help retain fresh-roasted flavor of coffee and nuts.
7. Prevent oxidation of spice oleoresins present in spices themselves and in seasoned foods.
8. Prevent oxidation of vitamins A, C and E in food.
9. Extend life of pharmaceuticals.
10. Inhibit mold in natural cheeses and other fermented dairy products.
11. Delay non-enzymatic browning of fruits and some vegetables.
12. Inhibit oxidation and condensation of red pigment of most berries and sauces.
13. Keep the smell and flavor of tea.
14. Prevent the segregation of salt, sugar, pepper, flour, etc.
15. Preserve the premium quality of wines after opening.
16. Prevent the moistening of crackers.
17. Retain the crunchy texture of biscuits, potato chips.
18. Do not change the taste of the food by adding lots of salt, sugar, or vinegar.
19. No more toxic chemicals.
20. Retain nutrition of food.

Because of our company's business interests, we would choose as our initial focus to develop food wraps to avoid water penetration. Cracker is chosen for consideration although the product can be used for other foods as well. The size of the cracker is assumed to be 2 in x 4 in, the number of cracker per package is 30, and the surface area and volume of the package is 52.5 in² and 18 in³, respectively. By daily experience, a cracker exposing to air of humidity of 80% starts to lose its crunchy texture in about 14 days. The amount of water vapor required to start moistening the cracker in 365 days would be $4\text{vol}\% \times 14/365 = 0.15\text{ vol}\%$. The following table summarizes the specifications of cracker preservation. The oxygen content is taken from the literature.

Table 13.2-1. Specifications of Cracker Preservation

Product	Cracker
Shelf life	1 year
Cost	Econom ical
Application conditions	Room temperature and pressure
Water vapor content	< 0.15%
Oxygen content	< 0.01%

PROJECT 3: Controlled Drug Release

All drugs have a minimum level below which they are not effective, and a toxic level above which they are harmful. This means that there is a finite window, called therapeutic limits, within which drug concentrations must be maintained. Conventionally, when drugs are ingested orally and digested, a rapid increase in blood concentration of the drug occurs, followed by a fairly sharp drop. The aim of a controlled drug release system is to permit prolonged drug delivery while maintaining drug concentrations within therapeutic levels. The Zoladex implant is used as a benchmark for product conceptualization. It is a 1 mm diameter cylindrical depot consisting of the drug suspended in a poly(lactide-co-glycolide) matrix. The drug loading is approximately 30 wt% and release occurs with polymer hydrolysis. Following are some of the basic requirements:

1. Zero order release over a period of time
2. Ease of sterilization
3. Minimal pain/discomfort
4. Ease of administration

PROJECT 4: Solid Formulation of Low Melting Point Active Ingredient

The safety and environmental impact of pesticides have long been of concern to the agrochemical industry. The pesticide components, known as active ingredients (AIs), having melting point ranging from 41 °C to 55 °C restricts the manufacture of pesticide to liquid formulation. Problems associated with such formulation include packaging contamination, excessive volatility, and use of organic solvents. Thus, it is highly desirable that solid formulation of active ingredients such as water dispersible granule (WG) be developed. Following are the basic needs:

1. Efficacious active ingredients; e.g., herbicides, and pesticides
2. Additional solid formulations other than WGs
3. Easier and less hazardous to handle

PROJECT 5: UV Shield Film

Our company has a strong background in multilayer coextrusion technology. We have numerous multilayer film products on the market, but have yet to tap into the glass surface area. Market survey reveals a strong demand for UV-filtering films for both home and automobile windows; in particular, a UV-reflecting film with an adhesive backing is of interest. Following are the basic needs:

1. UV elimination for home windows
2. Glare reduction for auto windows

3. Decrease UV transmission
4. No aesthetic defects
5. Easy application
6. Film thickness (70-150 microns)
7. Inexpensive relative to competitors
8. Transparent
9. Reduce heat gain

PROJECT 6: Adhesives for Wet Metal Surfaces

Joining metal together with itself or other surfaces such as plastics and fiberglass has always been an important step in the car manufacturing industry. The current method of metal joining includes the use of nuts and bolts, adhesives, and welding. However, these current methods have many problems including short shelf life, long curing time, high curing temperature, metal corrosion, and environmental pollution. In particular, significant surface treatment regarding the removal of monolayers of water on the metal surface leads to extra production costs. Also, in the last decade, there is an evolution towards the use of aluminum instead of steel in car production. It is highly desirable to come up with a new method of metal joining which is suitable for bonding all kinds of materials to the aluminum built cars. Following are the basic needs:

1. Join metal parts in automobile industry
2. Have to be applicable to aluminum
3. Shorter curing time
4. Does not build up pressure when it contacts with water
5. Does not require dry atmospheric room
6. Does not cause eye and skin irritation

Specifically, the following properties are targeted:

Table 13.2-2. Specifications of New Method for Metal Joining

Feature	Property
Application time	<3 hours
Working temperature	-50 °C –100 °C
Tensile strength	~1000 psi
Cost	Low
Others	Remove moisture on the surface

13.3. IDEAS

After identifying the needs, ideas for a winning product are required. Normally, it is useful to come up with as many ideas as possible from the customers, competitors, consultants and members of the product development team. From this list, we identify the best four or five ideas for further investigation. This can be done in two stages. First, the ideas are sorted to remove redundancy. Second, ideas that are inconsistent with corporate strategy, business unit strategy, or the competency that does not build on our corporate strengths are dropped. Additionally, one can use a concept-screening matrix to evaluate the general characteristics of each idea – chemical understanding, engineering requirements, and so on – and compare the weighted averages of these evaluations.

PROJECT 1: Optical Currency Substrate for Counterfeit Prevention

Recognizing the need for more sophisticated security features, our business goal is to use multilayer coextrusion technology to create an optical polymer substrate for U.S. currency. The ideas from brainstorming are sorted into categories as described below.

Minor Improvements to the Benchmark

1. Paper currency with irremovable polymer strip.
2. Machine-readable added to currency to tell how long it has been in circulation, and when it needs to be retired
3. Full multilayer optical property polymer currency
4. Multilayer polymer window in currency that diffracts light in a particular pattern
5. Anti-graffiti coating on currency to prevent the defacing of money
6. Florescent patches on currency
7. Anti-bacterial agent injected in outer polymer layer to reduce contamination of bills
8. Water-proof coating on paper money

Change in Substrate

9. Synthetic plastic currency stamped with optical ink
10. Polymer currency with different colors for the different denominations using dyed injected polymers
11. Metal coins that have a polymer core, lighter and cheaper

Optical Synthetic Polymers

12. Polymer currency with an inserted multilayer polymer optical window
13. Polymer currency with different colors for the different denominations using optical films with differing layer thickness to induce the color.
14. Polymer currency with burnouts to change the colors in particular areas

15. Make optical window in polymer currency of an unusual shape
16. Insert an optical window with burnouts to change colors
17. Machine-readable strips on polymer currency for use in vending machines
18. Paper currency with a polymer weave, more than one polymer strip woven into the bill

Adhesive Additions (These are products that use adhesive to attach them to the currency.)

19. Multilayer polymer, with optical properties, with adhesive backing placed on currency

Environmental Impact (These ideas involve recycling.)

20. Make currency from 100% recycled plastic
21. Polymer currency that can be recycled and made into something else

PROJECT 4: Solid Formulation of Low Melting Point Active Ingredient

The safety and environmental impact of pesticides have long been of concern to the agrochemical industry. The active ingredients (AI) of the pesticide component having melting point ranging from 41 °C to 55 °C restricts the product form of pesticide to liquid formulation. Problems associated with such formulation include packaging contamination, excessive volatility, and use of organic solvents. Therefore, the project team wants to develop promising solid formulations of active ingredients, which have the same ease of use of liquid products, but are easier and less hazardous to handle. The team has produced 38 ideas. Ideas that seem folly, vague, or redundant are labeled as F, V, or R, respectively.

1. Microencapsulation
2. Active ingredient in water soluble polymer
3. Form a sugar glass, using 3:1 sucrose to raffinose, and blend in the liquid.
4. Buoyant capsule (V)
5. Form an aerated tablet containing the AI, which effervesces with water
6. Bath ball technology
7. Use charged clay fillers
8. Gelatine host for the chemicals
9. Foil packaging (F)
10. Trap AI chemically in a polymer, with release triggered by water
11. Bio-degradable packaging
12. Freeze dried product (e.g. space food) (R-13)
13. Spray dried granulation of chemical
14. Oval shaped tablet (V)
15. Volcanic glass fillers (F)

16. AI in anhydrous fine solid
17. Use an antifreeze gel to hold the AI in suspension
18. Sugar coated solid particles
19. Black box (contains liquid AI with timed release, and dispersing capabilities) (F)
20. Use a porous bag containing the chemicals. Once filled, the pores are blocked with hydrophilic solid, e.g. sugar
21. Use a separate aeration tablet to disperse the AI in the tank
22. The “tea bag” idea, suspended by a string (F)
23. Sugar paper, holding the AI in matrix
24. “Bounce Paper” idea, non-soluble matrix holding the AI
25. Use magnetic fillers, along with a magnetic field in tank to help dispersion and reduce clogging of the nozzle
26. If ingredients have $-RCOOH$ or $-NH_2$ groups, react with acid or base
27. Capture the liquids in activated carbon
28. Capture the dispersed liquid in water glass (silicates) (F)
29. Capture the liquids in supercritically dried polyvinylalcohol
30. Covalently bond a non-volatile species to active ingredient.
31. Find an ink resin, which dissolves at any pH, but is not hygroscopic (F)
32. Disperse in wheat flour, dry and grind (F)
33. Jar of jellybeans, where the different AIs are held separately in solid particles and mixed together as required (R-2)
34. Hold in a water soluble jelly (R-2)
35. Put in a pH activated solid
36. Mix with other solids and form paste, like toothpaste. Then dry and granulate (F)
37. Dissolve in liquid crystals
38. Honeycomb (F)

The relatively sensible ideas are sorted into five categories. These include containment/package, encapsulation, incorporation, reaction/transportation and end concept. The ideas in *italics* are felt to be the most promising for the development of solid formulations of active ingredients.

Table 13.3-1. Sorted Ideas for Solid Formulations of Active Ingredients

Category	Idea
Containment /Package (Doubt over the stability of the containing package)	11. Bio-degradable packaging 20. Use a porous bag containing the chemicals. Once filled, the pores are blocked with hydrophilic solid, e.g. sugar
Encapsulation	1. Microencapsulation 6. Bath ball technology (not technologically mature)

		<p>18. <i>Sugar coated solid particles (environmental friendly)</i></p> <p>29. Capture the liquids in supercritically dried polyvinylalcohol (Disperse slowly because the outer layer is hard to dissolve)</p>
Incorporation	Amorphous	<p>2. <i>Active ingredient in water soluble polymer</i></p> <p>8. Gelatine host for the chemicals</p> <p>17. Use antifreeze gel to hold liquid AI in suspension (Good for controlling temperature and storage)</p>
	Rigid Matrix	<p>16. <i>AI in anhydrous fine solid (Low vapor pressure)</i></p> <p>23. <i>Incorporate active ingredient in sugar glass (Low vapor pressure and high dispersion rate)</i></p> <p>24. “Bounce Paper” idea, non-soluble matrix holding the AI (Doubts regarding the feasibility of the idea)</p> <p>35. <i>Put in a pH activated solid (promising)</i></p> <p>37. <i>Dissolve in liquid crystals (low vapor pressure)</i></p>
	Others	<p>25. Use magnetic fillers, along with a magnetic field in tank to help dispersion and reduce clogging of the nozzle. (It suggests the way to speed up the dispersion of AIs only)</p>
Reaction/Transportation (Lack of available information and lead to non-generic products)		<p>7. Use charged clay fillers</p> <p>10. Trap AI chemically in a polymer with release triggered by water</p> <p>13. Spray dried granulation of chemical.</p> <p>26. If ingredients have -RCOOH or -NH_2 groups, react with acid or base</p> <p>27. Capture the liquid in activated carbon</p> <p>30. Covalently bond a non-volatile species to active ingredient.</p>
End Concept		<p>21. Use a separate aeration tablet to disperse the AI in the tank (This idea is a modification at the final marketing stage.)</p>

PROJECT 6: Adhesives for Wet Metal Surfaces

The table below shows the ideas obtained by brainstorming. Those labeled as folly (F), vague (V), or redundant (R) are rejected.

Table 13.3-2. Ideas of Adhesives for Wet Metal Surfaces

1. Wipe the metal surface with cloth (F)	32. Invent coupling chemistry (V)
2. Change metal's composition	33. Adapt dental adhesives (V)
3. Change to a new adhesive (V)	34. Try a polymer with a protective layer and heat to use
4. Adhesive in water absorbing solvent	35. Use heat catalyzed polymer (V)
5. Use a plant that sticks to a ship (V)	36. Coat the surface before applying the adhesive (V)
6. Use natural rubber adhesive	37. Invent an adhesive that reacts with metal
7. Electrostatically charge the metal	38. Welding with a laser (F)
8. Put magnet in the current adhesive (R-7)	39. Replace the metal (F)
9. Use a super glue (i.e. a cyano acrylic)	40. Solder (F)
10. Use a different resin (V)	41. Use a sugar solution (V)
11. Make a resin with a hydrophilic part	42. Use a reversible glue (F)
12. Treat the surface with zeolite	43. Apply a vacuum adhesive (V)
13. Use a zinc coating primer	44. Use an adhesive developed for the bathroom (V)
14. Spray on a silicone coating	45. Use candles wax (F)
15. Use neoprenephenolic as adhesive (R-59)	46. Try water based adhesives (R-11)
16. Invent an adhesive that reacts with water	47. Use natural rubber (R-6)
17. Use silica gel for surface treatment (F)	48. Use spider web (F)
18. Choose a van der Waals bonding material	49. Use asphalt
19. Try ionic bonding (F)	50. Eliminate metal from cars (F)
20. Use water scavenger/adsorbing material in the adhesive base	51. Use rope to tie up the metals (F)
21. Treat the surface with alkali	52. Use bubble gum (F)
22. Use corn starch (F)	53. Make plastic or fiber glass cars (F)
23. Use an adhesive and a functional group that reacts with water	54. Don't use cars (F)
24. Use an isocyanate with water reactive part (R-23)	55. Use flower tapes (F)
25. Injects acidic salt in the metal (F)	56. Blow dry the surface
26. Use more adhesive (F)	57. Use toluene as the base solvent (R-4)
27. Use a concrete cement	58. Get water resistance by using nitrocellulose/polyisobutylene
28. Water catalyzed polymer	59. Use a phenolic group
29. Adherent with water reactive part (R-23)	60. Use a zipper (F)
30. Use a water scavenger adhesive (R-20)	
31. Add catalyst to speed up the reaction	

The remaining ideas are classified into five categories, with the more promising ones highlighted in *italic*:

Table 13.3-3. Sorted Ideas for New Metal Joining Methods

Category	Idea
Improvement in Existing adhesives	18. Choose a van der Waals bonding material (Weak bonding) <i>20. Use water scavenger/adsorbing material in the adhesive base</i> <i>23. Use an adhesive and a functional group that reacts with water (Reduce the surface treatment processes)</i> 31. Add catalyst to speed up the reaction (Not user-friendly as specific reaction conditions are required) 32. Coupling chemistry <i>43. Apply a vacuum adhesive (Low/moderate strength only)</i>
Water –Absorbing Adhesives	11. Make a resin with a hydrophilic part 16. Invent an adhesive that reacts with water (It is time-consuming and costly in doing research) <i>20. Use a water scavenger in the adhesive base (comparatively feasible and effective by adding zeolite to the adhesive)</i> 28. Choose a water catalyzed polymer
Surface Treatments	<i>13. Use zinc coating primer (Ensure clean surface for metal joining)</i> 14. Spray on a silicone coating 21. Treat the surface with alkali (Alkali may affect the product's performance) 34. Try a polymer with a protective layer and heat to use (Troublesome as heating of the polymer is required) 56. Blow dry the surface (Not user friendly and time consuming)
New Innovations	2. Change the metal's composition (It may affect the properties of metal for car manufacturing, especially strength) 6. Use a natural rubber (Weak bonding) <i>7. Electrostatically charge the metal (Well developed technology and not hazardous)</i> 37. Invent an adhesive that reacts with metal (Costly and time consuming in doing research) 58. Get water resistance with nitrocellulose/ polyisobutylene <i>59. Use a phenolic group</i>
Curiosities	27. Use a concrete cement 49. Use asphalt

13.4. SELECTION

After generating ideas to fill the needs, the next step is to select the best ideas for further development. In most cases, only a few ideas are selected, because of the substantial amount of work required to take an idea forward. Each potential product is evaluated in terms of technical feasibility and cost, competing products on the market and customers' wants. The concept selection matrix can be useful. A handful of important criteria weighted according to their perceived significance are generated to judge the ideas. All ideas are scored for each criterion, often relative to a benchmark that may be an existing product or well-established technology. An overall score for each item is then produced by summing the products of weighting factors and scores over all criteria. Two examples, Project 1 and 6, are presented below to show how to apply the selection matrix for product selection.

PROJECT 1: Optical Currency Substrate for Counterfeit Prevention

Along with the benchmark, the following four products are evaluated using selection matrix:

- A multilayer adhesive for authentication
- An optical currency substrate that uses multilayer technology
- A polymer currency substrate similar to the polypropylene Australian currency
- Surface treatment

A product's potential is assessed by grading them from 1 to 10 on the weighted performance criteria below:

Marketability: This includes both the size of the potential market and the acceptability of the product to consumers. Being the most significant obstacle, it is given the highest weight of 0.3.

Capital Investment: This criterion has a weighting of 0.1 because it is not desirable to spend excessive amounts on up front equipment.

Security Focus: Security focus has a moderate weighting of 0.15. While it is important to the overall goal of this project, these products all meet the security focus to some degree. Nonetheless, the optical currency should have a higher score because it would be nearly impossible to copy. The multi-layer adhesive would not add as much security because it might go unnoticed.

Durability: This criterion includes how long the product can be in circulation and its resistance to destruction. It is important for a product to be durable in order for a government or company to consider it.

Environmental Impact: Environmental impact would be more of a selling point than a make-or-break addition.

Company Technology: This is about whether the product utilizes the company's multilayer technology. It has a weighting of 0.15. The optical polymer should have a high score because the coextruded film does not require much knowledge of other technologies such as adhesives, etc.

Note that the benchmark is always given a score of 5. The category weights add up to a total of 1. The total score for each product is the sum of all the scores for each category multiplied by the corresponding weight. The following matrix is the final result. Note that the optical currency listed here is just the optical layer.

Table 13.4-1. Selection Matrix for Optical Currency Substrate

	Market-ability (0.30)	Capital Investment (0.10)	Security Focus (0.15)	Dur-ability (0.25)	Environ Impact (0.05)	Company Technology (0.15)	Total
Benchmark	5	5	5	5	5	5	5
Multilayer adhesive	8	3	6	5	2	7	6
Optical	6	2	9	8.5	8	9	7.23
Polymer	7	4	8	8.5	8	6	7.13
Surface treatment	7	4	5.5	7	1	5	5.8

The scores for the optical currency and the polymer currency are close at the top. With a more explicit security focus than plain polymer currency, the optical currency is the final choice.

PROJECT 6: Adhesives for Wet Metal Surfaces

Five weighted performance criteria are used in the selection matrix below:

Table 13.4-2. Selection Matrix for Wet Metal Surfaces Methods

	Weight	Benchmark	Electrostatic Charge	Coating Primer On Surface	Use Functional groups	Water Scavenger	Use Water Absorbing Solvent
Science & Technology	0.15	5	1	8	8	7	6
Effectiveness	0.35	5	7	5	7	6	5
Ease of Use	0.3	5	6	5	9	6	5

Cost	0.1	5	1	4	8	9	7
Environmental and Safety	0.1	5	3	6	6	7	7
Total score		5	4.8	5.45	7.6	7.0	5.55

The rationale for the assigned scores is given below:

Science and Technology: The functional group idea has the highest score because the technology is well developed. Information regarding the use of functional group such as moisture-cured urethane is readily available.

Effectiveness: Again, the functional group idea has the highest score. A functional group such as moisture-cured urethane has a shorter curing time (60 minutes @ 23 °C) when compared with other ideas. For example, polyurethane has a curing time of 4 hours. It has satisfactory tensile strength (~1000 psi), which meets the requirement for car manufacturing. It also creates good bonding to metals (especially aluminum), woods, plastics and fiberglass. This facilitates the bonding of different kinds of materials in aluminum built cars. In addition, it has a longer shelf life (12 months) when compared with the products of other ideas.

Ease of Use: A product based on a functional group such as urethane can be cured at room temperature. Without using a special room, this simplifies the application procedure. For other ideas, heating is usually required. For example, using zeolite as water scavenger, the application temperature is 177°C. Additionally, no surface treatment is needed for using functional group such as urethane because water serves as one of the reactants during the moisture-cured polymer reaction. Therefore, this solves the moisture problem on metal surface during application.

Cost: The price of water scavenger, for example zeolite, is low.

Environmental and safety: Water scavenger such as zeolite is non-toxic. On the contrary, other ideas cause harmful effects to human and the environment. For example, the use of functional group, such as moisture-cured urethane, involves diisocyanate.

The method of using functional group comes out on top for the following reasons:

1. It reacts with water on the metal surface. This minimizes surface treatment.
2. It requires much shorter curing time than the benchmark.

3. It is applied at room temperature without using a pre-heating process.
4. Long shelf life allows time for shipping and storage.
5. It has satisfactory tensile strength.

13.5. PRODUCT MANUFACTURE

At this point, the final specifications for the one or two chosen product(s) after selection process should be identified. This can be done using a three-step procedure. First, we define the product micro and macrostructure. Second, we rank the product's most important attributes, an effort that forces a review of how the product will be used. Third, we review any chemical triggers, that is, chemical stimuli which cause major changes in product properties. Finally, we turn to the manufacture itself, which relies on technical know-how of thermodynamics, chemical reaction kinetics, transport phenomena, and unit operations. Some of these ideas are illustrated in the following example. Except for a schematic of the manufacturing process, the many details related to the manufacturing plant are omitted in this discussion.

PROJECT 1: Optical Currency Substrate for Counterfeit Prevention

Final product specifications

Multilayer coextrusion technology is used to create an optical polymer substrate for U.S. currency. The final product specifications of the optical currency are listed below:

1. The core film consists of the multilayer, two-polymer design, which is proprietary to the company.
2. The current intaglio ink process is not altered.
3. The bill would look similar to the current U.S. bill to ease the transition to a new substrate.

Product design

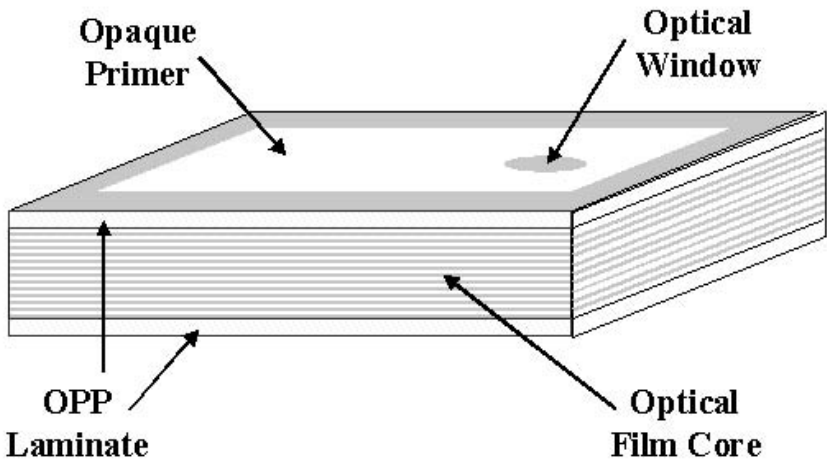
The new currency substrate consists of three main components: an optical film core, an oriented polypropylene (OPP) laminate applied to both surfaces, and an opaque acrylic receptor coat. A simplified diagram of this construction is shown below.

Component specifications

Optical film core

The multilayer film of the optical core produces a green reflector. The visual effects of the green reflector are not easily reproduced, yielding the easily identified security feature. Possible raw materials are polystyrene (PS), and polymethylmethacrylate (PMMA). There is a substantial difference in refractive

index (1.59 for PS and 1.49 for PMMA) and good interfacial adhesion properties between them.



Final Product Form

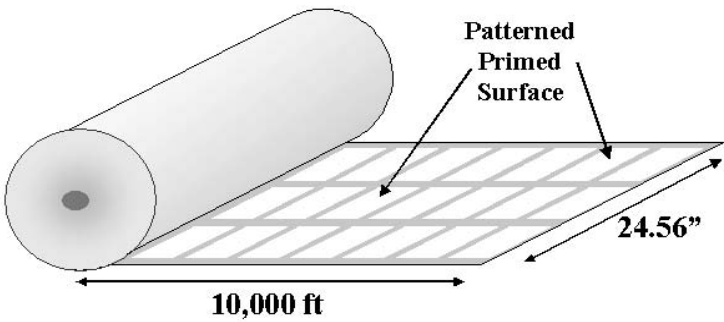


Figure 13.5-1. Schematic of New Currency Substrate

OPP laminate

It protects the vulnerable optical core and provides mechanical strength and durability to the construction. It should have the following attributes:

1. It has a thermally activated bonding adhesive ideal for polymer substrate applications.

2. Its total film thickness (including the adhesive) is 33 μm , leading to a total product thickness of 132 μm .
3. The light transmission is 99%.
4. Excellent folding characteristics
5. The oriented polymer chains provide a moderate level of rigidity to the substrate.
6. Resistant to many types of chemicals, such as detergents, gasoline, and dry-cleaning solvents.
7. High gloss finish.

Primer coating

It promotes adhesion of intaglio inks to the polypropylene surface. An acrylic based primer is a good choice because of its ability to effectively bond water-based inks. Dry powder form of acrylic primer is diluted with methyl ethyl ketone and xylene (each component is mixed in equal parts by weight). To create the opaque surface, 5wt% titanium dioxide pigment is added to the solution.

Manufacturing plant

The schematic below shows the equipment units that are required for the manufacturing process.

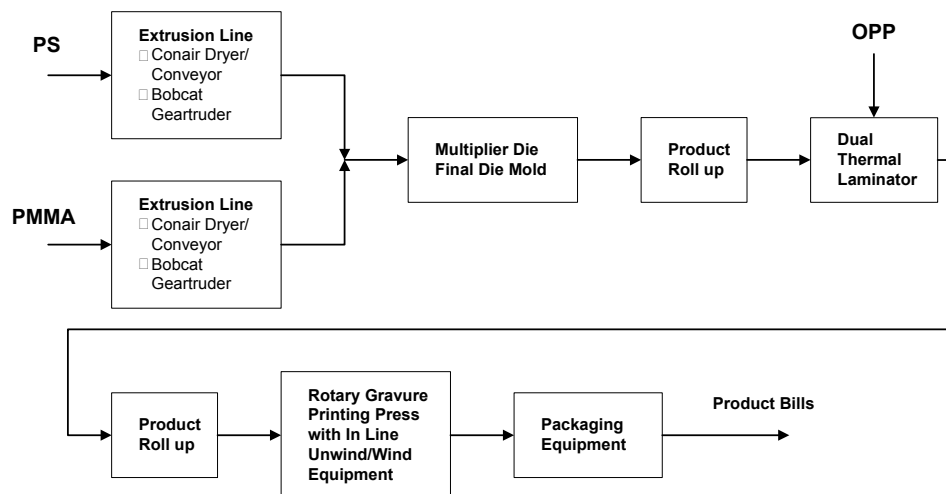


Figure 13.5-2. Manufacturing Process Flow Diagram

6. CONCLUSIONS

In this chapter, diverse examples were used to illustrate a four-step procedure for the design of chemical products. First, the basic needs for each product are identified. Six individual examples including plastic money, food wrap, controlled release drugs, solid herbicides, UV shield film and metal adhesive have been considered. Then, product ideas generated by brainstorming are sorted and screened to remove redundancies and follies. The examples involving plastic money, solid herbicides and metal adhesive are used to illustrate this step. The remaining ideas are classified into different categories for further selection. The selection matrix can be used to quantify the advantages and disadvantages of the sensible ideas and to identify the best idea. Finally, we turn to the manufacture of the product. The optical currency serves as an example to explain some of the issues in product manufacturing including final product specifications, product construction, component specifications and manufacturing process flow diagram.

Chapter 14

Case Studies in Chemical Product Design – Use of CAMD Techniques

Rafiqul Gani

*CAPEC, Department of Chemical Engineering, Technical University of Denmark
Building 229, DK-2800 Lyngby, Denmark*

14.1 Introduction

The objective of this chapter is to provide the reader with a selection of chemical product design related problems (case studies) highlighting the tasks where computer-aided molecular and mixture design (CAMD) techniques can be employed. Other computer-aided tools to be used are primarily methods for property prediction (product evaluation), product-process modeling (performance evaluation) and process simulation (design & verification). All computer-aided tools used in this case study were developed at CAPEC and are available as toolboxes within ICAS (Integrated Computer Aided System) – Gani (2002a). The solutions for all the problems presented in this chapter are not given. Interested readers can obtain the detailed solutions for all problems from the author.

14.1.1 Computer-Aided Molecular-Mixture Design: Brief Overview

Computer aided molecular design (CAMD) problems are defined as, *Given* a set of building blocks and a specified set of target properties; *Determine* the molecule or molecular structure that matches these properties.

In this respect, CAMD technique [Gani et al. (1991)] is the reverse problem of property prediction, where, given the identity of the molecule (or the molecular structure) or a mixture, a set of target properties is calculated. In this chapter,

the Hybrid CAMD technique developed by Harper et al. (2001) and implemented in ProCAMD (2002b) will be used.

The solution of all CAMD problems, can in principle, be divided into the following four main steps.

Step 1: Problem Formulation – here, the CAMD problem is defined in terms of target properties (both the identity of the property as well as their target values).

Step 2: Initial Search - generate initial list of candidates through a search of a database (if available, for example, CAPEC database). This provides a good idea of which types of molecules one should be looking for. Note that the search should be made only with respect to the pure component target properties as a search with respect to mixture properties may not be possible.

Step 3: Generate and Test - use any CAMD technique (and software, for example, ProCAMD) to automatically generate and test candidates. The selected CAMD technique should be able to generate molecular structures and evaluate their properties with respect to the specified target properties.

Step 4: Verification – here, the selected candidates are further analyzed in terms of their performance when they are applied for their designed use. Models capable of simulating their performance in their process of application are needed. These models may be process simulation models (for example, ICASSIM or ICAS-utility) as well as product application models (such as delivery of an active ingredient).

14.2 Case Study 1: Solvent Design-Selection

A mixture of acetone and chloroform is to be separated into pure products [Hostrup et al. (1999)]. Since they also form an azeotrope, one alternative to satisfy the separation objective is to find a suitable solvent for separation by extractive distillation. This type of problem in product design is usually encountered during the purification or recovery of products, by-products, reactants or removal of undesirable products from the process. Also, it can be noted that failure to find a suitable solvent may result in the discard of the product. Alternatively, a functional chemical product manufacturer may be interested to find, design and develop a new solvent. In this case, the solvent is the chemical product.

14.2.1 Solvent Identification with ProCamd

First an analysis of the binary mixture of acetone and chloroform is made to obtain the relevant data. A selection of the most important data needed for this case study is listed in Table 1.

Table 1: Properties from analysis of the acetone-chloroform mixture

Property	Property Value	
	Acetone	Chloroform
T_b [K]	178.45	209.63
T_m [K]	329.44	334.33
δ_T [(MPa) ^{1/2}]	19.73	18.92
Known solvents	Water, ethanol, ethyl ether	Ethanol, ethyl ether
Azeotrope composition at 1 atm and 345 K	0.344	0.656

Note that a high-boiling azeotrope is formed between acetone and chloroform. The above problem description and mixture analysis helps us to define the CAMD problem.

14.2.1.1 Step 1

We would like to find a solvent that breaks the azeotrope between acetone-chloroform (or moves the azeotrope point sufficiently to one side to allow separation by distillation) so that high purity acetone and chloroform can be recovered by extractive distillation. The solvent should be more selective to chloroform than acetone. The solvent, acetone and chloroform must form a totally miscible liquid. The solvent must not form azeotrope with either acetone or chloroform. The solvent should be easy to recover and recycle. The solvent should have favorable EH&S properties.

14.2.1.2 Step 2

Since the solvent is selective to chloroform, a preliminary search in the database could be made to find known solvents for chloroform that are also miscible with acetone. Using the CAPEC database [Gani (2002a)], a list of known solvents, if satisfying the search criteria stated above, can be found. Figure 1 shows the solvents found within the database.

casno	Chemname	mw	Tb	SolPar
000064-19-7	ACETIC-ACID	60.05	391.05	19.0078
000126-98-7	METHACRYLONITRILE	67.09	363.45	19.094
000078-93-3	METHYL-ETHYL-KETONE	72.11	352.65	18.8787
000071-43-2	Benzene	78.11	353.15	18.7296
000110-83-8	CYCLOHEXENE	82.15	356.05	17.4235
000110-02-1	THIOPHENE	84.14	357.15	20.1206
000505-22-6	1,3-DIOXANE	88.11	379.25	20.6721
000123-91-1	1,4-DIOXANE	88.11	374.65	20.5354
000110-01-0	TETRAHYDROTHIOPHENE	88.17	394.15	20.4608
000616-44-4	3-METHYLTHIOPHENE	98.17	388.65	19.5471
000554-14-3	2-METHYLTHIOPHENE	98.17	385.75	19.3765
000108-91-8	CYCLOHEXYLAMINE	99.18	407.15	18.8281
000080-62-6	METHYL-METHACRYLATE	100.12	373.65	18.5308
000123-54-6	ACETYLACETONE	100.12	411.15	19.5267
000565-69-5	ETHYL-ISOPROPYL-KETONE	100.16	386.65	17.3251
000108-10-1	METHYL-ISOBUTYL-KETONE	100.16	389.65	17.4328
000108-38-3	m-XYLENE	106.17	412.25	18.0535
000106-42-3	p-XYLENE	106.17	411.45	17.9031
000095-47-6	o-XYLENE	106.17	417.65	18.3923

Figure 1: List of solvents from database search

Based on the above information, the CAMD problem definition is revised as follows – The solvent can be acyclic hydrocarbons and ketones (aromatic compounds, chlorides, dioxanes are not considered for EH&S concerns). The normal boiling point should be higher than that of chloroform (334 K), the molecular weight could be between 70-120, the solvent must not form azeotrope with either acetone or chloroform, and, must be totally miscible with the binary mixture of acetone and chloroform.

14.2.1.3 Step 3

Set-up the solvent design/selection problem defined in step 2 in ProCAMD. In ProCAMD, the information related to the CAMD problem is organized in terms of the following types:

- General problem control: Define the type of molecules to be designed, the size of the molecules, to include isomers or not, etc.
- Non-temperature dependent: Specify upper, lower, and/or goal values only for the target properties (a collection of 26 properties are available)
- Temperature dependent property: Specify upper, lower, and/or goal values only for the target properties together with the temperature (a collection of 6 properties are available)

- Mixture property: Define the model to be used for liquid activity coefficient calculation, specify the binary mixture (composition, temperature, pressure), select the solute to be extracted, the type of phase equilibrium calculation (VLE or LLE) and finally, specify desired solvent performance related properties (solvent power, selectivity, etc.)
- Azeotrope/miscibility calculations: Specify if the solvent must or must not form azeotropes, miscibility as a liquid solution, solid precipitation, etc.

For the case study, the following specifications are needed:

General problem control

- Design acyclic compounds containing groups of C, H and O atoms (select all molecule types with C, H & O atoms)
- The size should be from 4 to 8 groups and with maximum 1 functional group
- Select the “perform database search after generation”

Non-temperature dependent

- Use molecular weight from 70 to 120 g / mole. (uncheck “goal”)
- Normal boiling point from 340 to 420 K. (uncheck “goal”)

Temperature dependent property

No “temperature dependent properties” needs to be specified.

Mixture properties

- Specify the azeotropic mixture as the feed mixture (0.344 acetone and 0.656 chloroform) at 345 K and 1atm.
- Specify a minimum selectivity of 1.7 for chloroform
- Select Chloroform as Solute.

Azeotrope/Miscibility calculations.

- For azeotrope calculation specify that the designed compound should not form azeotropes with any of the compounds in the mixture.
- Miscibility calculation may be made at fixed amount of solvent, calculations at intervals are not necessary, and the final mixture of acetone-chloroform and solvent must be totally miscible.
- Mass ratio of generated compound should be 3 times (by weight) with respect to chloroform.

Start calculations & Results from ProCAMD

After the execution has been completed, ProCAMD provides the results in terms of a “summary” of the molecular design based search as well as detailed results for each candidate solvent. Figure 2a shows the “summary” for the problem described above while Figure 2b shows the detailed results for one candidate solvent.

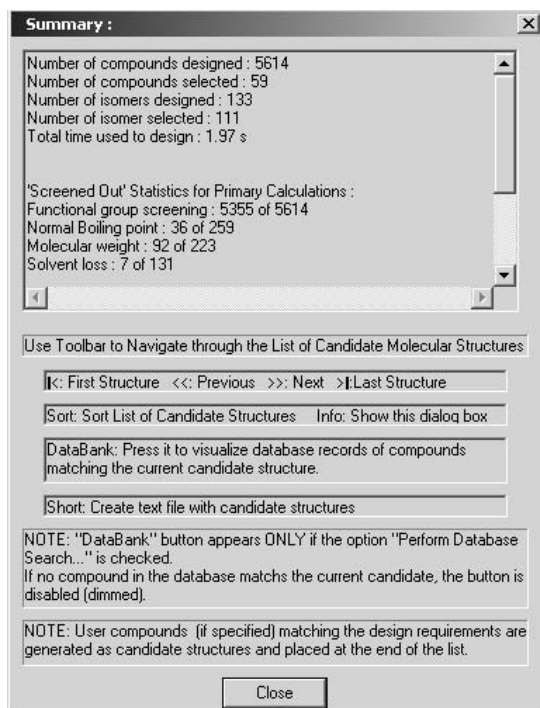


Figure 2a: Results summary from ProCAMD

It can be noted from Fig. 2a that ProCAMD needed only 1.97 seconds to generate 5614 molecular structures and after evaluating them ended-up with 111 feasible candidates. The time also includes the process calculations related to miscibility, azeotrope verification as well as solvent loss and selectivity.

Compound 110 :

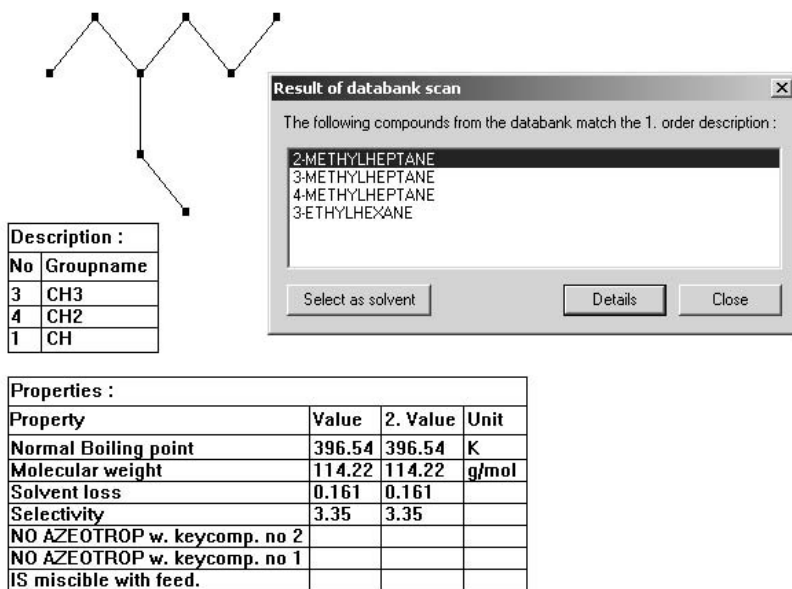


Figure 2b: Detailed results for a feasible solvent candidate found by ProCAMD

14.2.1.4 Step 4

Here, process simulation needs to be performed to verify the solvent performance. ICAS [Gani (2002a)] provides tools for design of the extractive distillation columns (PDS-tool) as well as rigorous simulation and optimization (ICASSim & ICAS-opt). In this case study, only the final flowsheet obtained through PDS-tool and the simulation results obtained through ICASSim are highlighted. Note that this part could, in principle, be done through any other process simulation software. Figures 3a and 3b show the flowsheet and the corresponding simulation results. It can be noted from Fig. 3b that the desired separation has been achieved.

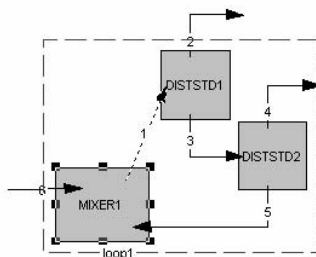


Figure 3a: Designed flowsheet for the acetone-chloroform separation

STREAM NUMBER	1	2	3	4
TEMPERATURE (K)	350.00000	332.04270	373.15131	342.63881
PRESSURE (atm)	1.00000	1.00000	1.00000	1.00000
ENTHALPY (K/Kmole)	-27615.86917	-24505.51626	-26910.01571	-14287.60495
ENTROPY (K/Kmole)	41.50294	35.62145	44.69363	37.41181
U-ENERGY (K/Kmole)	-27616.02699	-24532.76285	-26910.18654	-14315.72103
DENS. (Kmole/m ³)	6.33628	0.03670	5.85403	0.03557
VAPOUR FRACTION	0.00000	1.00000	0.00000	1.00000
LIQUID FRACTION	1.00000	0.00000	1.00000	0.00000
(Kmole/hr)				
ACETONE	10.00039	9.05476	0.94563	0.94524
CHLOROFORM	10.98840	0.85620	10.13220	9.14408
2-METHYLHEPTANE	89.89447	0.06853	89.82593	0.93118
TOTAL	110.88325	9.97949	100.90376	11.02051

STREAM NUMBER	5	6
TEMPERATURE (K)	369.00747	350.00000
PRESSURE (atm)	1.00000	1.00000
ENTHALPY (K/Kmole)	-27545.64659	-19114.10880
ENTROPY (K/Kmole)	47.80138	36.69383
U-ENERGY (K/Kmole)	-27545.83081	-19142.82893
DENS. (Kmole/m ³)	5.42629	0.03462
VAPOUR FRACTION	0.00000	1.00000
LIQUID FRACTION	1.00000	0.00000
(Kmole/hr)		
ACETONE	0.00039	10.00000
CHLOROFORM	0.98811	10.00000
2-METHYLHEPTANE	88.89475	1.00000
TOTAL	89.88325	21.00000

Figure 3b: Verification by simulation of the flowsheet of Fig. 3a.

14.2.2 Related Problems

- Find solvents to separate acetone from methanol separation (VLE separation) – replace chloroform with methanol, identify the mixture properties and then set-up the solvent design-selection problem as highlighted above.

- b. *Find solvents for methyl acetate from methanol separation (VLE separation)* – here replace acetone with methyl acetate in the mixture from problem a and follow the same procedure.
- c. *Find all binary mixtures that form an azeotrope with ethanol at 1 atm pressure and where the second compound is a cyclic compound, with $300\text{ K} < T_b < 500\text{ K}$* – here, solvents are not being searched. Instead, all compounds that are totally miscible with ethanol and forms an azeotrope with ethanol at 1 atm are being sought. This is a simple example of mixture design.
- d. *We have a water stream that is contaminated with phenol (0.0142 mole fraction of phenol in water). We need to remove the phenol through solvent-based liquid-liquid extraction. The solvent must be totally immiscible with water and dissolve the phenol. The extraction operation will take place at 298 K and 1 atm. Find an environmentally friendly solvent.* – this problem is similar to the case study and problems a & b with the only difference that liquid-liquid phase equilibria is involved instead of VLE.
- e. *We have phenol deposits as a solid and we need to clean the equipment before our product can be produced. We already know that we can use benzene or toluene to dissolve the phenol. We would like to investigate if it is possible to use a more environmentally friendly anti-solvent to extract the phenol* – this problem is also similar to the above problem but here, solid-liquid equilibria is involved instead of LLE or VLE. Other similar problems, find solvents (anti-solvents) to extract by crystallization, the following compounds – Naphthalene, Ibuprofene (see chapter 4), Diuron (CAS number 330-54-1) and Crabazole (CAS number 86-74-8).
- f. *Solvents for organic synthesis* – A good collection of problems on this topic can be found in Gani et al (2005) and Gani et al. (2006).

14.3 Case Study 2: Backbone Generation

In this case study, we will start with a known molecule (for example, Corticosterone), use the property estimation features in ProPred [Marerro (2002)] to create free attachments in the molecule (that is, create a backbone). The Backbone is then transferred to ProCamd, where terminated structures will be generated. In this way structures of “synthetic candidates” of a lead biologically active compound may be identified through molecular design.

14.3.1 Step 1

Start ProPred from ICAS and draw the molecule (or import the mol-file of the molecular structure or specify the SMILES string)

14.3.2 Step 2

ProPred draws the molecule and predicts the properties (as shown in Figure 4a)

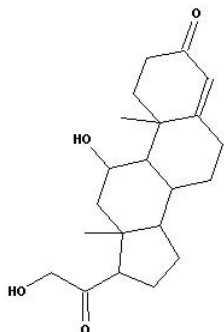


Figure 4a: Molecular structure of Corticosterone (000050-22-6)

Summary Marrero and Gani Constantinou and Gani Joback and Gani				
Property Values estimated by using methods included in ProPred				
Compound Name : Corticosterone				
Compound CAS : 000050-22-6				
Compound Smiles : OCC(=O)C1CCC2C3CCC4=CC(=O)CCC4(C)C3C(O)C2				
Compound Formula : C21H30O4				
Mw (g/mol) : 346.46				
Best estimates are suggested for each property according to developers' criteria. See detailed estimates through each in the corresponding pages				
WARNING: Accuracy of some estimated properties (e.g. Hansen parameters) might be poor if the melting point is far above 298 K				
Property	Method	Unit	Est. Value	Exp. V
Tm	MG	K	455.30	454.1
Tb	MG	K	690.57	N/A
Tc	MG	K	922.59	N/A
Pc	MG	bar	18.82	N/A
Vc	MG	cm ³ /mol	1083.09	N/A
Zc	MG		0.266	N/A
Gf[298K]	MG	kJ/mol	-404.20	N/A
Hf[298K]	MG	kJ/mol	-911.63	N/A
omega	CG		1.324	N/A
Hv[298K]	*****	kJ/mol	N/A	N/A
Hv[Tb]	MG	kJ/mol	128.18	N/A
Hfus	MG	kJ/mol	45.80	N/A
Sfus	MG	J/(mol*K)	100.86	N/A
Vm[298K]	*****	cm ³ /mol	N/A	N/A
Vm[Tb]	MG	cm ³ /mol	431.69	N/A
Sol. Par.[298K]	MG	MPa ^{1/2}	25.62	N/A
Refractive Index	MG		1.89	N/A
Molar Refraction	*****		N/A	N/A
Surf. Tens.[298K]	*****	dyn/cm	N/A	N/A
G.T. Temp.	*****	K	N/A	N/A
Log(Kow)	MG		2.41	1.94
Log(WS)	MG	Log(mg/L)	1.82	2.29
Closed Flash Temp.	CG	K	534.57	N/A
Open Flash Temp.	CG	K	606.27	N/A
Hansen Disp. sol.	CG	MPa ^{1/2}	16.49	N/A

Figure 4b: Predicted properties of Corticosterone

14.3.3 Step 3

Using the drawing tools in ProPred, remove the OH group connection from the molecular structure at the two locations (as shown in Figure 4c).

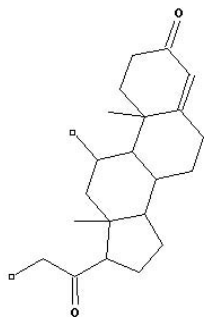


Figure 4c: Backbone with two-free attachments.

14.3.4 Step 4

Launch ProCamd from ProPred from the tools menu in ProPred.

14.3.5 Step 5

Fill-out the necessary problem definition pages in ProCamd (general problem control, non-temperature dependent properties) as shown below in Figure 4d.

14.3.6 Step 6


Terminate the backbone by clicking on “GO”. Among the 10 different candidates, compound 2 (which is Corticosterone) is shown in Figure 4e.

Azeotrope/Miscibility Calculations		Biodegradation Calculations	
Temperature depd. props.		Mixture Properties	
General Problem Control		Non temperature depd. props.	
Problem Title:			
Title <input type="text"/>			
Generate:			
<input checked="" type="radio"/> Acyclic Compounds <input type="radio"/> Aromatic Compounds <input type="radio"/> Cyclic Compounds		<input checked="" type="checkbox"/> Generate Isomers Autoslack in initial generation: <input type="text"/> <input type="text"/> <input type="text"/> $\pm 10\%$	
Preselection:			
<input checked="" type="checkbox"/> Generate Alcohols <input checked="" type="checkbox"/> Generate Ketones <input checked="" type="checkbox"/> Generate Aldehydes <input checked="" type="checkbox"/> Generate Acids <input type="checkbox"/> Generate Phenols <input type="checkbox"/> Generate Compounds containing silicon <input type="checkbox"/> Generate Compounds containing double bonds <input type="checkbox"/> Generate Compounds containing triple bonds <input type="checkbox"/> Generate Compounds containing fluorine <input type="checkbox"/> Generate Compounds containing chlorine <input type="checkbox"/> Generate Compounds containing bromine <input type="checkbox"/> Generate Compounds containing iodine <input type="checkbox"/> Generate Compounds containing sulphur		<input type="checkbox"/> Generate Esters <input type="checkbox"/> Generate Ethers <input type="checkbox"/> Generate Amines <input type="checkbox"/> Generate Amides	
Selected Groups:		BackBone:	
<input type="text"/> CH3 CH2 CH C OH CH3CO <input type="text"/> CH2CO CHO COOH		<input type="checkbox"/> BackBone Generation Min. Free: <input type="text"/> 0 Max. Free: <input type="text"/> 0	
<input type="button" value="Edit Groups"/>			

Azeotrope/Miscibility Calculations		Biodegradation Calculations	
Temperature depd. props.		Mixture Properties	
General Problem Control		Non temperature depd. props.	
ProPred properties	Min:	Max:	Goal:
Molecular Weight (g/mol):	<input type="text"/> 340	<input type="text"/> 0	<input type="text"/> 0
Normal Melting Point (K):	<input type="text"/> 350	<input type="text"/> 0	<input type="text"/> 0
Total Solubility. Param. (MPa ^{1/2}):	<input type="text"/> 22	<input type="text"/> 25	<input type="text"/> 0

Figure 4d: ProCAMD problem formulation for generating completed structures for the specified backbone.

Compound 2 :



Description :	
No	Groupname
2	CH3
6	CH2
5	CH
2	C
1	CH=C
2	OH
2	CH2CO

Figure 4e: Completed backbone in ProCAMD

Properties :			
Property	Value	2. Value	Unit
Solubility parameter at 298 K	23.71	23.71	MPa ^{1/2}
Normal Melting point	355.21	355.21	K
Molecular weight	346.45	346.45	g/mol

14.3.7 Related Problems

- *Generate backbone in ProCamd and terminate (manually) in ProPred* - In this problem, we will first generate a backbone with ProCamd using only the C & H atoms and with 1 free-attachment in the backbone. We will then go to ProPred to draw the molecular structure and work on the structure without terminating the structure. We will then launch ProCamd from ProPred to find the final terminated structure through ProCamd. All the generated structures will also need to satisfy a set of property targets (melting point, solubility parameter and the octanol-water partition coefficient).
- *Design a large molecule having the following properties, $M_w > 300$; $T_b > 400\text{ K}$; $T_m > 300\text{ K}$* – This problem is solved with ProCAMD in the first step by simply asking for all types of molecules satisfying only the three specified property targets. Once these are generated, it is possible to work further with these through ProPred, where manually other atoms and bonds are added to evaluate the properties of the generated molecules.

14.4 Case Study 3: Polymer Design

A polymer film is needed to protect an electronic device [Seider et al. (2003)]. The device will operate at temperatures below 333 K and must be protected by a fairly dense layer that absorbs small concentrations of water. A design team has prepared the following quality specification: density = 1.5 g/cm³, glass transition temperature = 383 K (50 degrees above the operating temperature), and water absorption = 0.005 g/g polymer. As stated initially by Derringer and Markham (1985), candidate molecular groups, together with their group contributions (for target property estimations) are given in Table 2.

Table 2: Group contribution values for estimation of the polymer properties

Group number	Group name	Y_i	V_i	H_i	M_i
1	CH ₂	2700	15.85	0.000033	14
2	CO	27000	13.4	0.11	28
3	COO	8000	23	0.075	44
4	O	4000	10	0.02	16
5	CONH	12000	24.9	0.75	43
6	CHOH	13000	19.15	0.75	30
7	CHCl	20000	29.35	0.015	48.5

In the above table, M_i , V_i , Y_i and H_i are the contributions for group i for estimating the molecular weight, the molar volume, the glass-transition temperature, and the water absorption, respectively. The model equations for each of these properties are as follows:

Molecular weight, M (gm/mol)

$$M = \sum_{i=1}^7 M_i n_i$$

Molar volume, V (cm³/mol)

$$V = \sum_{i=1}^7 V_i n_i$$

Density $\rho = 1/V$

Glass transition temperature, T_g (K)

$$Y = \sum_{i=1}^7 Y_i n_i$$

$$T_g = Y / M$$

Water absorption, W (gm_{water}/gm_{polymer})

$$H = \sum_{i=1}^7 H_i n_i$$

$$W = 18H / M$$

14.3.1 Step 1

Generate polymer repeat units with minimum 2 groups and maximum 4 groups.

14.3.2 Step 2

Estimate the target properties for each generated polymer repeat units and eliminate those that do not match the target property values. For the remaining polymers, evaluate them in terms of the following selection criteria:

$$\left(\frac{\rho - \rho^{spec}}{\rho} \right) + \left(\frac{T_g - T_g^{spec}}{T_g} \right) + \left(\frac{w - w^{spec}}{w} \right)$$

The polymer repeat unit with the smallest value is the best polymer, in this simple polymer design problems. Table 3 highlights the values for the target properties and the selection criteria for 6 polymer repeat units and the best polymer is highlighted.

Table 3: Designed polymers with the group contribution method

Polymer	ρ	T_g	W	Selection criteria
-CH ₂ -CHCl-	1.383	363.2	0.0043	0.026766
-(CHCl) ₂ -	1.652	412.5	0.0056	0.029073
-CH ₂ -(CHCl) ₂ -	1.489	384.7	0.0049	0.000748
-(CHCl) ₃ -	1.652	412.4	0.0056	0.029073
-(CH ₂) ₂ -(CHCl) ₂ -	1.383	363.2	0.0043	0.026766
-(CHCl) ₄ -	1.652	412.4	0.0056	0.029073

14.3.3 Related Problem

Simultaneous design of membrane-based gas separation and the design of the polymeric membrane – In this problem, a membrane-based pervaporation model is used to calculate the target properties for the design of the polymeric membrane. This step actually also designs the pervaporation processes as for a given mixture to separate and a specified product recovery, the details of the polymeric membrane in terms of its properties (permeability, surface area, volume, etc.) are calculated. Using these calculated values as targets, in the next step, a polymer design problem (similar to the one given above but with different properties) is formulated and solved. A detailed solution of problems of this type can be found in Soni et al. (2006), who highlights an application example for selective recovery of oxygen from air through pervaporation with

polymeric membranes. Soni et al. (2006) found several polymers that satisfy the target properties. A detailed solution of the problem can also be obtained from the author.

14.4 Case Study 4: Refrigerant Design

It is desired to find a replacement for Freon-12 as an alternative refrigerant [Duvedi & Achenie (1996)]. The objective is to find replacements that have the same refrigerant related properties as Freon-12 but without the harmful environmental properties (such as the Ozone depletion potential) - The new refrigerant must absorb heat at temperatures as low as -1.1°C and reject heat at temperatures as high as 313 K. It must also respect the following characteristics:

- Must not polymerize.
- Be nonflammable.
- Assure that if there are leaks, they are from the refrigeration system.
- Allow a compression ratio below 10.
- A small amount of refrigerant must allow a transfer of the heat.
- A small amount of refrigerant must flash into the valve.
- Choice of the specifications for ProCAMD

The following specifications are necessary to solve the problem through ProCAMD:

- To ensure that the refrigerant does not polymerize, compounds that have double or triple bonds will be avoided.
- To ensure that the refrigerant is nonflammable, compounds involving both nitrogen and halides will be avoided.
- To ensure that if there are leaks, they are from the refrigeration system, desirable refrigerant must have a vapor pressure greater than 1.4 bars (0.4 bar of security are taken with the atmospheric pressure). As vapor pressure increases with temperature, solvent must verify: $P_s(271\text{ K}) > 1.4\text{ bars}$.
- A compression ratio below 10 means that the following expression is checked: $P_s(43.3^{\circ}\text{C}) < 14\text{ bars}$.

Also, to reduce the amount of refrigerant needed, the latent heat of vaporization must be as high as possible. The latent heat of vaporization of Freon12 is 18.4kJ/mol, so to assure that the new refrigerant is at least as good as the

Freon12 and knowing that the latent heat of vaporization decreases with temperature, the refrigerant must check:

$$\Delta H_v(271 \text{ K}) > 18.4 \text{ kJ/mol.}$$

$$C_{pl}(293 \text{ K}) < 134.6 \text{ J/(mol K)}$$

The problem can be solved using the discretization method discussed in chapter 4 of this book. First candidates are generated using the normal boiling points and the normal boiling point. In the next stage, the remaining properties are calculated only for the molecules that have not been discarded.

As reported by ProCAMD, it generated 1206 replacement candidates, out of which 565 were initially selected. This gave rise to 559 structures, out of which 289 were found to be acceptable.

The generated list of compounds that could be potential replacements of Freon-12 are given in Table 4.

Table 4: Feasible refrigerant replacement solvents.

	Ps (bars) at 271 K	Cpl (J/(mol K)) at 293 K	Ps (bars) at 313 K	Hv (kJ/mol) at 298 K
CCl ₂ F ₂ = FREON 12	3.08	117.8	11.28	19.4
CH ₃ Cl	2.19	79.4	9.00	21.80
C ₂ H ₂ F ₄	2.69	134.8	10.16	19.7
C ₂ H ₆ O	3.16	109.3	12.66	20.8
C ₂ H ₃ ClF ₂	1.60	123.4	10.28	27.9
C ₂ H ₅ FO	1.34	123.1	5.02	20.6
C ₂ H ₂ ClF ₃	1.46	137.1	5.18	19.5
C ₃ H ₇ F	2.12	125.2	6.97	18.1
C ₄ H ₁₀	1.50	138.9	5.81	20.8

Finally, the Ozone Depletion Potential (ODP) can be calculated with the following models:

Molecules that have one carbon atom:

$$ODP = 0.585602 n_{Cl}^{-0.0035} e^{M / 238.563}$$

Molecules that have two carbon atoms:

$$ODP = 0.0949956 n_{Cl}^{-0.0404477} e^{M/83.7953}$$

Based on the above model for ODP, CH₃Cl is removed from the list of refrigerant alternatives together with all other compounds with chlorine. Finally, the two compounds C₂H₆O and C₄H₁₀ are kept for further studies as possible replacements.

14.5 Other Problem Definitions

14.5.1 Active Ingredient Design/Selection

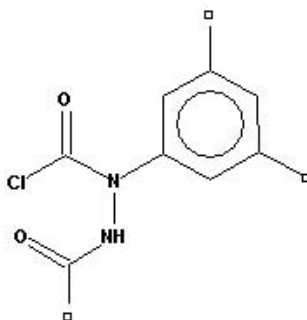
α -chloroacetamideochloroacetanilides is a herbicide that have the remarkable property of stunting the growth of turf grass without killing the grass while enriching the green texture of the turf. These compounds are referred to as “turf retardants”. Experiments have been performed to measure the biological activities measured as the decrease in vertical growth of the turf grass tall fescue. These activities were then correlated to the LogP of the various relatives of α -chloroacetanilide. Table A in appendix lists the values of the activities and the corresponding LogP of the molecules.

Determine the following:

- a) Use the values given in the table to estimate the coefficients for the following correlation

$$A = d + e\text{LogP} + f(\text{LogP})^2$$

- b) Generate completed structures from the backbone of the α -chloroacetamideo-chloroacetanilides given below (generate at least 15 structures). R1 could be hydrocarbons (acyclic and cyclic) while R2 and R3 should be only acyclic hydrocarbons with 1-3 carbon atoms.



- c) Estimate the LogP of the generated completed structures
- d) Identify the structure with the highest activity

14.5.2 Drug Design

The drug barbiturate is a well-known drug. It has different forms, mostly different types of barbituric acid - a list of barbituric acids are given below together with the CAS-numbers.

- Candidate 1: 000077-02-1
- Candidate 2: 061346-87-0
- Candidate 3: 000076-94-8
- Candidate 4: 091430-64-7
- Candidate 5: 001953-33-9
- Candidate 6: 007391-69-7
- Candidate 7: 090197-63-0
- Candidate 8: 017013-41-1
- Candidate 9: 027653-63-0

Analyze each of the compounds and calculate their Octanol-Water partition coefficients. Use the following two models to estimate the molar concentration (C) of the compound,

- To produce a 1:1 complex with protein (binding to bovine serum albumin)

$$\text{Log}_{10}(1/C) = 0.58 \log_{10}P + 0.239$$

- To calculate the hypnotic activity of the compound in rabbits after subcutaneous injection

$$\text{Log}_{10}(1/C) = 2.09 \log_{10}P - 0.63 (\log_{10}P)^2 + 1.92$$

Find which form of barbituric acid has the best (lowest concentrations) in both cases. For the best barbiturate molecule, find a solvent which is miscible with water.

14.5.3 Mixture Design (Additive for Paints)

For a specific paint application, a mixture of solvents is needed. The mixture is going to be identified by its ability to mix with water (total miscibility), normal boiling point (determines the solvent evaporation rate), the solubility parameter (determines if it is soluble in the paint) and molecular weight (size the candidate molecule).

For mixture properties, use the following linear mixing rules:

Molecular weight: $M_{Wm} = \sum x_i M_{Wi}$

Boiling point: $T_{bm} = \sum x_i T_{bi}$

Hildebrand solubility parameter: $\delta_{Tm} = \sum x_i \delta_{Ti}$

In the above equations, subscript i indicates compound i and subscript m indicates the mixture value.

For following upper and lower bounds for each property as well as the target values, find how many binary mixture satisfy the target and find the minimum cost binary mixture.

Molecular weight: $41 < M_{Wm} = 85 < 151$

Boiling point: $350 < T_{bm} = 370 < 559$

Hildebrand solubility parameter: $20 < \delta_{Tm} = 25 < 34$

The cost function can be defined as,

$$F = \sum x_i C^* \rho_i$$

Where, C is a cost factor (=1000 \$) and ρ_i is the density of compound i.

Note: To generate the candidate molecules, you may use any database of your choice. Out of the compounds found, if the following 5 compounds appear, select them in the short list of 10 compounds.

Acetonitrile
Ethyleneglycol
Morpholine
2-Butoxyethanol
Triethyleneglycol

14.5.4 Mixture Design

For some process application, it is necessary to find mixtures that are not miscible in water, is liquid at the operating condition (around 300 K and 1 atm) and can absorb heat (that is, has a high heat capacity). Find the mixture with the highest heat capacity (in the liquid phase).

Determine the following:

- Formulate the general mixture design problem as an optimization problem providing all relevant equations for the objective function and constraints.
- Suggest a decomposition scheme
- Solve each decomposed sub-problem (before the final optimization sub-problem)
- Order the binary mixtures with respect to their heat capacities to identify the optimal solution.

The mixture is going to be identified by its ability to not mix with water (total immiscibility), normal boiling point (each compound in the mixture has a T_b above 350 K so the mixture will be a liquid), normal melting point (each compound in the mixture has a T_m below 250 K so the mixture will be a liquid), the Hildebrand solubility parameters of each of the compounds should be between 18-22 MPa^{1/2} (so the two compounds are mutually miscible).

For mixture properties, use the following linear mixing rules:

Molecular weight: $M_{wm} = \sum x_i M_{wi}$

Boiling point: $T_{bm} = \sum x_i T_{bi}$

Boiling point: $T_{mm} = \sum x_i T_{mi}$

Hildebrand solubility parameter: $\delta_{Tm} = \sum x_i \delta_{Ti}$

In the above equations, subscript i indicates compound i and subscript m indicates the mixture value.

14.6 Conclusions

A collection of case studies for chemical product design highlighting some of the tasks where systematic model-based approaches can be applied, has been presented. All the case studies have been solved by the author and his coworkers using the methods and software tools developed in-house. Interested readers can obtain the detailed solutions from the author as well as licenses for the software tools used. It can also be noted that the process related issues have not been highlighted in the case studies. This is intentional as the objective for the case studies presented in this chapter has been to highlight mainly the product related issues through the use of CAMD techniques. As many of the unit operations found in the food processing, pharmaceutical and agrochemical industries, for example, are still not available, the objective of current and future work is to fill this gap.

References

- Duvedi, A. Achenie, L. E. K., 1996, Designing environmentally safe refrigerants using mathematical programming, *Chemical Engineering Science*, 15, 3727-3739.
- Gani, R., Nielsen, B., Fredenslund, Aa., 1991, A Group Contribution Approach to Computer-Aided Molecular Design, *AIChE Journal*, 37 (9), 1318-1332.
- Gani, R. 2002a, *ProCAMD Manual*, PEC03-25, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).
- Gani, R., 2002b, *ICAS Documentation*, PEC02-14, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).
- Gani, R., Jimenez-Gonzalez, C., Constable, D. J. C., 2005, Method for selection of solvents for promotion of organic reactions, *Computers & Chemical Engineering*, 29, 1661-1676.
- Gani, R., Jimenez-Gonzalez, C., ten Kate, A., Crafts, P. A., Jones, M., Powell, L., Atherton, J. H., Cordiner, J. L., 2006, A modern approach to solvent selection, *Chemical Engineering*, March, 30-43.

- Harper, P. M., Gani R., Kolar, P., Ishikawa, T., 1999, Computer aided molecular design with combined molecular modelling and group contribution, *Fluid Phase Equilibria*, 160, 337-347.
- Marrero, J., 2002, *ProPred Manual*, PEC02-15, CAPEC Internal Report, (Technical University of Denmark, Lyngby, Denmark).
- Seider, W. D. Seider, Seader, J. D., Lewin, D., 2003, *Product & Process Design Principles Synthesis, Analysis, ad Evaluation*, (2nd edition), Wiley.
- Soni, V., Abildskov, J., Jonsson, G., Gani, R., 2006, Structural design of polymers for membrane based separation processes using reverse simulation approach, *Computer Aided Chemical Engineering*, (in press).

Appendix

Table A: List of measured biological activity of the turf versus the LogP of the API

A	LogP	A	LogP	A	LogP
62	3.29	53	4.04	74	3.21
0	4.88	26	4.14	67	2.99
70	3.22	5	5.32	65	3.22
53	4.28	14	7.11	70	2.84
10	6.05	28	4.66	70	2.73
56	4.05	19	7.99	13	4.55
30	3.84	16	4.46	65	2.70
49	4.06	7	6.28	64	2.68
0	6.40	53	4.15	61	2.46
46	3.82	3	4.62	60	2.52
65	3.75	0	4.69	68	2.46
0	4.93	0	1.99	0	5.34
35	4.13	49	3.56	3	7.46
65	3.52	49	1.73	42	4.81
42	1.52	62	2.40	36	2.91
33	3.56	60	1.44	34	3.96
71	2.70	57	1.97	0	5.87
49	3.82	52	3.79	47	3.39
60	3.49	52	3.26	21	2.29
63	3.09	72	1.97	36	2.23
67	2.17	66	3.02	3	5.52
67	3.85	66	2.49	15	4.73
72	3.05	41	0.79	54	3.08
44	2.76	63	3.02	38	3.61
72	3.52	75	1.48	8	4.99
42	4.02	65	2.49	43	3.17
30	4.00	70	1.95	28	3.73
40	4.02	61	1.79	0	6.05
74	3.74	53	2.36	44	3.67
21	3.56	58	2.89	50	2.56
16	6.93	60	2.89	5	2.63
37	3.69	41	3.42	53	2.91
69	3.26	12	0.87	34	1.15
46	3.96	28	0.88	52	2.93
61	2.75	21	2.59	45	1.5
65	2.76	50	2.47	58	2.03

Chapter 15

Nature of Chemical Products

Luis A. Cisternas

*Chemical Engineering Department, University of Antofagasta, Casilla 170,
Antofagasta, Chile*

15.1 INTRODUCTION

There exists a body of knowledge for chemical processes. Clearly, there should be a similar one for chemical products. To improve our knowledge of chemical products, it would help to have some kind of classification which guides its development and teaching. Thus, the main aim of this chapter is to examine the nature of chemical products. This subject encompasses a wide spectrum of issues. I would like to share my thinking on these issues with you.

This study is motivated by the recent interest in the area of chemical product design [1-6]. Much has been written about the challenges and opportunities for chemical engineers in this area [7-8], the necessity of incorporating this subject matter in the training of chemical engineering professionals [9-11], and particularly, the challenges to process systems engineering [12-16]. Part of the discussion has been on how to make good use of the experience and the knowledge accumulated for chemical process design in the development of chemical product design. It is natural to develop new knowledge by building on what already exists. In fact, recent advances in chemical product design follow the two approaches used in process design. An optimal solution is obtained by searching among a collection of alternatives through mathematical optimization (e.g. [17]), and systematic reduction of alternatives through heuristics (e.g. [18]).

In retrospect, there is a consensus that the development of process engineering has passed through four eras: industrial chemistry, unit operations, chemical engineering science, and chemical systems engineering. In the era of industrial chemistry (before 1925), research was focused on chemical industries for the

manufacture of sulfuric acid, soda ash, gasoline, etc. The second era, referred to as unit operations (1925-1950), was characterized by the study of operations such as distillation, heat transfer, grinding and other similar ones [19]. After that, a new paradigm focusing on an understanding of the most important principles emerged and was referred to as the era of chemical engineering science (1950-1975). Aspects such as transport phenomena, thermodynamics, kinetics, design and control of processes became the basic elements of a more scientific body of knowledge. The fourth era, in which we are now, involves process systems engineering. It considers aspects such as process integration and process-product integration. The introduction of unit operations made it possible to study separately aspects such as separations, heat transfer, and reactions.

The development of engineering sciences allows a better understanding of each unit operation, thereby identifying a better way to do process design. In my opinion, these aspects are very important for the development of chemical product engineering; that is, divide the products to identify their constituent parts and their nature in order to achieve development in this area.

As in process design, this is a complex task. It has been necessary to develop particular strategies for each kind of problems. Thus, strategies have been developed for the design of fractional crystallization [20], distillation [21], energy integration [22], mass integration [23], reactors network [24], among others. In other words, strategies for designs have been developed depending on the technology used (distillation, crystallization), or depending on the kind of problem to solve (separation, energy integration, chemical reaction).

In the case of product design, strategies based on the application of the product are observed; that is, specific products such as refrigerants, solvents, pastes, and so on have been studied. However, in chemical product engineering, we do not have a theory as in chemical process engineering. For example, in chemical process engineering one of the more important elements is the flow sheet, which has been very useful in the development of the area. A similar graphics element is not available for chemical product engineering.

The challenge of this chapter then is to clarify the nature of chemical products, give the basic definitions related to a chemical product and see how these definitions can be useful for the classification, study and design of chemical products.

15.2 SOME OBSERVATIONS OF THE NATURE OF CHEMICAL PRODUCTS

In this section, we will propose some definitions about chemical products and identify some attributes or special features of chemical products.

Chemical Product: A chemical product is a complex arrangement of parts, ordered and interconnected. In other words, a chemical product consists of different units that form a system. According to Webster's Dictionary, a product is "something produced, especially something grown or manufactured." This implies that it does not make sense if a product is produced without taking into consideration its function. Thus, a chemical product can be defined as a system formed by different chemical substances, which is manufactured for one or more purposes.

Components: Because a chemical product consists of different chemical substances, we can distinguish two kinds of products, single and compound. For example, we can distinguish a single product every time we deal with an entity without distinguishing components. The single product is characterized just for the properties in which the entity appears as a whole. While different parts can form a single product and each part can contribute to the properties of the single product, one of those parts cannot be responsible for the observed properties by themselves. For example, methanol can be considered as a single product, since it is characterized by a series of properties, boiling point, viscosity, and so on. These properties belong to it as a whole. Although we can identify many parts such as the OH, CH₂ and CH₃ groups, none is responsible, by itself, for a methanol property. Then, we can say that a single product has just one component.

We recognize compound products when distinguishing substances inside the compound product, which is responsible by itself for at least one compound product property. We will call these substances the components of compound products. Each component can be a single product or another compound product. On the other hand, we can distinguish in the compound product some properties that belong to it as a whole. Thus, a compound product is formed by components; it has some properties that are component properties and some properties belong to the compound product as a whole. For example, a soap bar possesses properties that are attributed to only some of their components, such as fragrances or surfactants. Other properties depend on their microstructure, the way in which the components are distributed among the different phases present.

Organization and structure: The organization is constituted depending on how the different components are included, having the desired properties, in order to

make a component work. Therefore the organization of a product defines its identity. If the organization changes, the identity will be lost and the product will cease to exist. At least the components, properties, and structures will take part in the organization of a chemical product. Notice that desired properties in a product can be either constant or variable.

The relation between the components that form a chemical product, constitute the structure of the product. The structure of a chemical product can change without changing its identity as a chemical product. This is because the characteristics of the components or even the relation between the components may change, while maintaining the desired properties of the chemical product (whether constants or variables), and the organization. For example, in motor oil, one of the properties corresponds to viscosity, which must be inside a certain range despite the change in temperature. To get this polymethacrylates or polyisobutylenes molecules are used, which change their microstructure while the temperature changes, getting the improvement of the oil viscosity, and therefore maintaining the product properties.

Environment: As mentioned previously, a chemical product has to be produced for a particular function. Its existence is determined in the presence of the environment that it interacts with. This is to say, different from a chemical substance, the chemical product needs an environment to be defined. There is no empty space; there must be a system and an environment. Therefore, this environment also needs a definition, which is established in the application field, and market for a particular chemical product.

A chemical product interacts with its environment through its properties. The compound products interact in two forms: single and compound chemical products. Some properties belong to the chemical products, independent of the environment, but some other properties depend on the environment that they interact with.

When there are properties that are environment dependent, we say that there is a complementary between the product and the environment. This complementary can be positive if the interaction helps to improve the product properties. There can also be a negative complementary when the environment-product interaction degrades the product properties.

The environment-product interaction also leads to changes in the condition of both the product and the environment, which can be chemical and/or structural. This environment-product transformation focuses on the product when the chemical and/or structural changes are mainly produced in the product. The chemical and/or structural changes can be mainly produced in the environment, situation in which the product influences the environment.

Niche: The section of the environment with which a particular property of the chemical product interacts is referred to as niche. For example, a pesticide can have as the environment the plant, the atmosphere, and the human beings. The pesticide interacts with the environment through its properties. There are different kinds of interaction depending on the niche. For example, some properties such as the contact area depend on the surfactant characteristics and the surface of the leaf. The niche is the surface of the leaf. The absorption of the pesticide depends on the characteristics of the layers, like the cuticle [25]. In this case, the niche consists of the layers of the plant's leaves. Also, the diffusivity of the active product in the layers of the plant leaves corresponds to a property that depends on the environment-product interaction. Some other pesticide properties, such as solubility of the active agent in the solvent, do not depend on the environment.

From the product life cycle viewpoint, the product niches will change during processing, storage, shipping, distribution, re-processing, use, recycling and/or disposal. For pesticide design, all the niches in the life cycle can be important.

Properties: As we have observed, an essential element in chemical products are their properties, basically because they are sold and bought for what they do. Some of these properties belong to components that form the chemical product, and others belong to the chemical product as a whole. Usually, the latter properties are those that depend on the chemical product microstructure. Some properties do not depend on the environment with which they interact and some others do. Figure 1 shows the type of interactions that occur between the chemical product and the environment.

A chemical product property must be observable, measurable or otherwise known characteristics related to the product. Therefore, when a property cannot be measured or when there is not a clear definition, then congruent properties are required with the desired property. This is especially important when the environment is the human being because the product properties depend not only on the closest characteristics of the niche, but also on human being tastes and preferences.

In addition, chemical product properties can be classified into structural and functional. Examples of structural properties are density, viscosity, size, and shapes, whereas examples of functional properties are safety, smooth, skin protection, and adhesion to surface. It is clear that the structural properties will depend on the structure and components of the chemical products, whereas the functional properties are more related to the interaction product-environment.

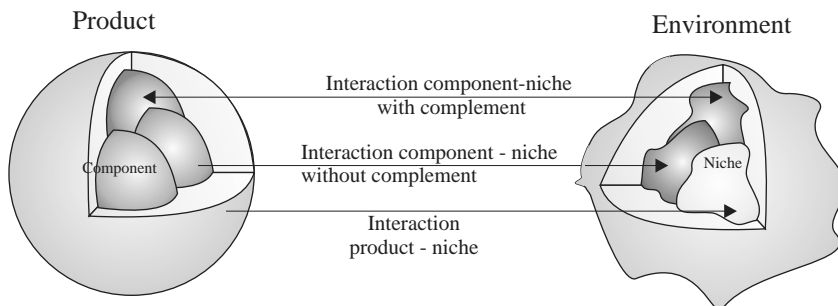


Figure 15.2-1. Chemical product interaction (properties).

Process-product interaction: Since a chemical product has to be produced, it is clear that a production process is required. When the product properties depend on the process, we say that the chemical product is dependent on the process. Otherwise, we say that the chemical product is independent on the process. This distinction is important in the design. In the former, the product and process design should be made simultaneously, whereas in the latter, the product and process design can be done independently. We will see how useful these definitions can be in the following sections.

15.3. CHEMICAL PRODUCTS CLASSIFICATIONS

The development of chemical products has been led by the industry. Not surprisingly, the language that is used has served to the necessities of the company and the market. That is why product classifications have been ambiguous and changing through time [26]. For example, chemical products had been classified based on the prices and uses.

The classifications by prices are not appropriate, because prices change with the changes in the market. The classifications by use, for example, specialty chemicals, chemicals specialties, intermediates, fine chemicals, are not only ambiguous, but also can change because of market strategies. There can be many names for similar products. For example, in fertilizers, we find many denominations such as specialty fertilizer, fertilizer specialties, nutrient fertilizer, packaged fertilizer, customer-formula fertilizer, and commercial fertilizer. A more meaningful classification helps in studying fertilizer products. Using the definitions of the previous section, it is possible to classify the chemical products, taking into consideration the number of components, the characteristics of structures, and the interaction with the environment. For

example, Figure 15.4.-1 shows an illustration of these three classification criteria. A product can be considered as single or compound according to the number of components. Solvents can be single products in some case, whereas the formulations are compound chemical products.

Regarding their organization, chemical products can be classified between those in which their properties are the sum of the components properties, and in which some of their properties are properties of the product as a whole. In the first group, there are products that do not depend on the structure and interaction of each component. In the second group, we can identify those that depend on that structure. Finally, we can classify the products, taking into consideration whether or not there is complementary with the environment.

In Figure 15.4-2, each point represents a kind of chemical product. For example, point number 5 represents chemical products, which are compound products with complementary to the environment, and where the properties are basically the properties of each product component. Usually, the products of the type number 1 are the simplest, whereas the products of the type number 8 are the most complex. Of course, products of the type number 1 can be more difficult to design than the type number 2, for example, big and complex molecules. Figure 3 shows examples of chemical products according to this classification.

It is also possible to consider sub-classifications depending on whether the complementary is positive or negative, occurs in the environment or in the product, or is produced in niches.

15.4 DESIGN OF CHEMICAL PRODUCTS

Chemical products are designed through several stages, which can be classified into four stages with interrelation as shown in Figure 15.4-3. These steps are: development of conceptual design, search, physical prototype and manufacture.

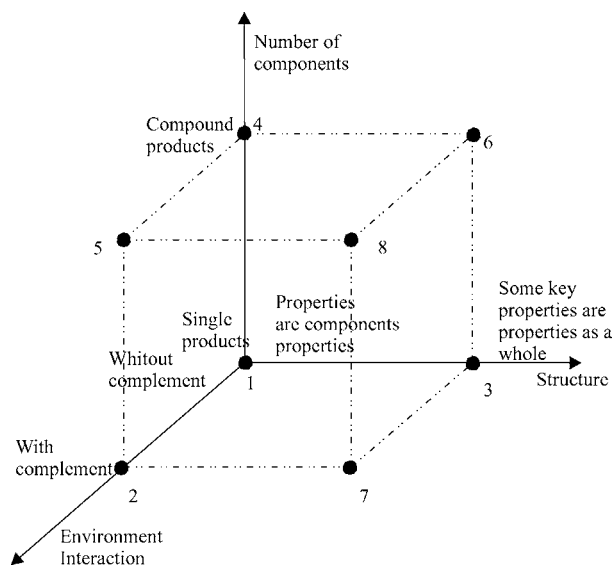


Figure 15.4-1. Chemical Product Classification.

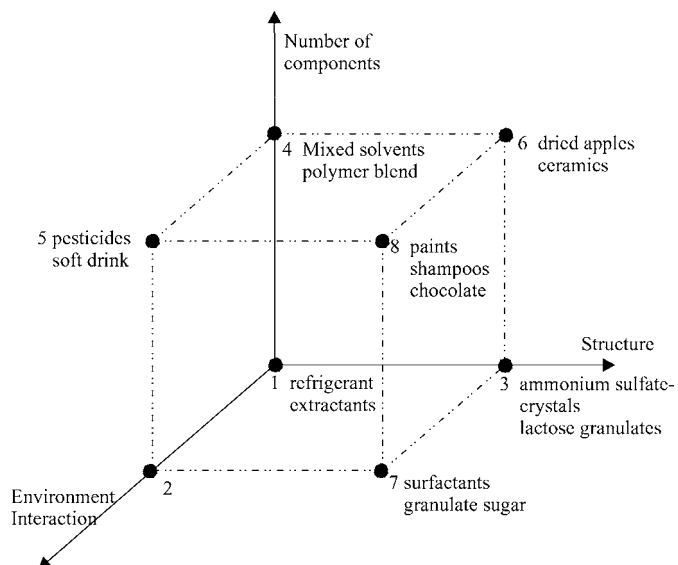


Figure 15.4-2. Examples of Chemical Products.

The conceptual design consists of identifying the technical specifications of the product, both structural and functional requirements. The design specifications can be derived from the demands for a completely new product, complaints about the functionality of existing products, or the failure due to malfunctions of existing products. In search, ideas that allow carrying out the specifications of the conceptual design are identified. This stage depends on the strategies used in each company, their information sources, and the technologies controlled. The physical prototype consists of the design in a laboratory level of the product, which is developed by experimentation, experience, knowledge, priority, and evaluations against different criteria and design specifications. Manufacture, corresponds to the production improvement of the chemical product. The first three stages are used to define the product that will be manufactured, and the fourth stage is concerned with how to produce it. As indicated in Figure 15.4-3, these stages are repetitive, even in the final stage of manufacture, because of an introduction of new technologies, uncertainty in the market and resources of the company.

These stages of design have been previously identified by Cussler & Moggridge [27], and in some way, it summarizes the six stages identified by Hill [4] for structured products. However, in Figure 4 the interactions that occur between the different stages have been emphasized. This make chemical product design an ill-structured problem because a chemical product may have some performance in addition to those used in defining design specifications. These performances may be in disagreement with the already generated solution, and therefore the problem is subject to continuous redefining. Also, the interactions take into account the dynamic nature of product design.

The definitions in the first section of this chapter can be useful in many ways for design, especially in the stages of search, physical prototype and manufacture. For example, the classifications of Figure 15.4-1 can help to establish the order in which different decisions related to the product must be made. For example, the procedure for a product of type 5, can start by identifying the components that contribute to the properties that are not complementary with the environment. In a second stage, we identify the most appropriate components for the complementary properties with the environment.

The definitions and classifications can help in the same way to each specific stage in Figure 15.4-3. In the stage of search, for example, the definitions can help to identify in a better way the necessities and the required properties. For example, if it is desired to improve any property that is complementary to the environment, the identification of the niche or niches may help to identify the appropriate ingredient, or to include a pretreatment or a post-treatment which modifies the niche characteristics, before or after using a product. This is what

is carried out when using a pretreatment for dyed hair before applying the shampoo, or when using fabric softener after washing clothes.

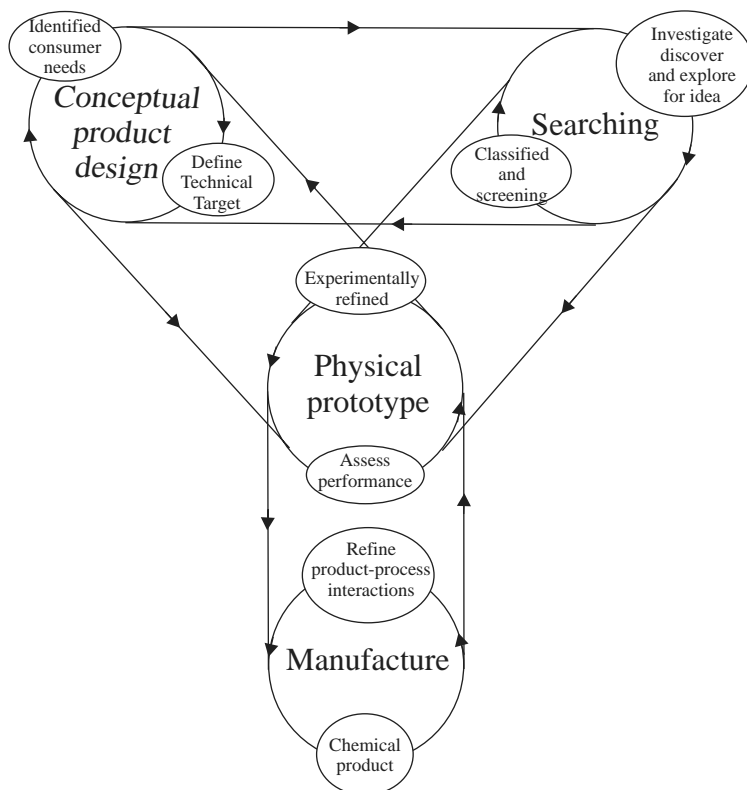


Figure 15.4-3. Chemical Product Design Process

As mentioned, chemical product design requirements can come about because of desires for a totally new product, complaints about the functionality of existing products, and/or the failure due to malfunctions of existing products. Therefore, there are several kinds of chemical product design problems. For instance those ruled by structural decisions, those ran by functional decisions and those that depend on both factors. Let us consider the design of perfumes to explain theses cases.

Perfumes are complex mixtures of substances having dissimilar chemical properties. Considering one of the most important properties, from the perfumer viewpoint, the volatility, there are a large range of materials, classified into three classes: Top notes or initial fragrance impression, body notes or middle

notes, and end notes, base notes or dry out. Top notes are the more volatile compounds; they can be in a perfume only a few minutes; body notes give the character to a perfume and can endure a few hours; end notes are the less volatile compounds which can endure more than eight hours and are used as fixatives of the top and body notes. One of the difficulties that a perfumer faces is the right choice of each fragrant compound, not in a pure solution, but its behavior in a perfume mixture. The art of perfumery consists of combining a wide range of raw materials to create a harmonious, pleasant, and expressive fragrance. Generally, this choice is based on trial and error experiments and subjective judgments.

Searching for a structure

Consider a quaternary liquid mixture, neroli oil, geraniol, citronellol and solvent, having different volatilities. Neroli oil represents a top note, citronellol and geraniol are body notes. The solvent is ethanol diluted with water to the required concentration. Let us consider this mixture as a base perfume to which musk ketone (4-tert-butyl-2,6-dimethyl-3,5-dinitroacetophenone) is added as an end note or fixative.

Although the behavior of the base perfume, and thus the odor value (OV) of each component, can be known, the OV in the new mixture will change because the OV depends largely on the solvent and the remaining aromatic components present in the perfume mixture. This is due to molecular size and in great extent to physical interactions at the molecular level, such as polarity forces (i.e. ion-dipole, dipole-dipole, hydrogen bonding forces, and others), in other words to the structure.

The intensity of a fragrant compound i can be expressed in terms of its odor value, OV_i , which is defined as:

$$OV_i = \frac{C_i^g}{Thr_i} \quad (1)$$

where C_i^g is the concentration of component i in the headspace and Thr_i is the threshold concentration. The threshold concentration is defined as the lowest concentration at which a chemical compound can be distinguished with certainty from a blank under standard conditions. The OV_i can be evaluated as [28]:

$$OV_i = \gamma_i x_i \left(\frac{P_i^s M_i}{Thr_i} \right) \left(\frac{1}{RT} \right) \quad (2)$$

In this equation x_i is the liquid perfume concentration, M_i the molecular weight, R the ideal gas constant, and T the absolute temperature. Equation 2 relates the liquid perfume composition, x_i with the human sensory reaction of the evaporated perfume. A key factor of Equation 2 is the activity coefficient, γ , because it represents the affinity of a molecule to its neighboring medium. High value of γ means an increased inclination for a given substance to be released from the mixture and low value of γ means a low concentration in the headspace. This means that the OV values of a particular component can change if it is diluted in different solvents or mixed with different fragrance components.

Consider that the odor perception by human nose is correlated with the odor value, OV_i , in the headspace above the liquid. If a specific OV_i distribution values is wanted, the perfume composition can be determined with the help of Equation (2). This methodology can facilitate the optimization of perfume compositions, reducing in this way some trial and error time and chemical wastes. Clearly, the problem is determined by structural decisions because the perfume composition depends on the interaction of the different perfume components.

Searching for a new niche

Perfume, like other chemical products, follows a life cycle composed of introduction, growth, maturity, and decline. To change the life cycle companies use different strategies to shift products in the maturity phase back or catapult new products forward into growth phase. For instance, a perfume in the maturity phase can be changed to a radically different category to shift the product to a growth phase. The search for the new niche is run by functional decisions.

If the new niche for the perfume is its use in cosmetics, toiletries or household product, then the niche-product interaction becomes very important. Perfumes are used specifically for their odor whereas in these new niches several new factors must be considered. For example, the perfume oil used in creams must not cause discoloration; the fragrance used in a powdered detergent must be alkali resistant; a fabric softener is expected to leave clothes with a pleasant odor; and even a household cleanser must have a pleasant and functional odor, although active chlorine places difficulty on the stability of the perfume oil. Of course, decisions can affect or modify the product (perfume) or the niche (e.g. creams).

15.5 CONCLUSIONS

This chapter has attempted to analyze the nature of a chemical product. It is an entity with different chemical substances, manufactured for one or more applications. Along with other descriptions and definitions, this promotes an understanding of how the product is formed, its organization, and how it interacts with the environment.

Based on these definitions and descriptions, classification of chemical products can be performed in a more scientific way, without ambiguities and/or overlap. These classifications should help to understand the nature of some products and to organize their study. This preliminary approach is expected to give examples and/or methodologies of design using these principles in the near future.

REFERENCES

1. J.M. Prausnitz, 1999, Thermodynamics and other chemical engineering sciences: old models for new chemical products and processes, *Fluid Phase equilibria*, 158-160, 95-111.
2. G.D. Moggridge & E.L. Cussler, 2000, An introduction to chemical product design, *Trans Écheme*, 78 (A), 5-11.
3. L.F. Gladden, C. Buckley, P.S. Chow, J.F., Davidson, M.D. Mantle, A.J. Sederman, 2004, "looking into" chemical products and processes, *Current Applied Physics*, 4, 93-97.
4. M. Hill, 2004, Product and Process Design for Structurated Products, *AIChE J.*, 50 (8), 1656-1661
5. J. Abidskov & G.M. Kontogeorgis, 2004, Chemical Product Design: A new challenge of applied thermodynamics, *Chemical Engineering Research and Design*, 82(A11), 1505-1510
6. N. Muro-Suñé, R. Gani, G. Bell, & I. Shirley, 2005, Predictive property models for use in design of controlled release of pesticides, *Fluid Phase equilibria*, 228-229; 127-133
7. W. Rähse, 2004, Produktdesign-Möglichkeiten der produktgestaltung, *Chemie Ingenieur Technik*, 76(8), 1051-1064
8. W. Rähse, S. Hoffmann, 2003, Product design-Interaction between chemistry, technology and marketing to meet customer needs, *Chemical Engineering & Technology*, 26, 9-18
9. M. Kind, 1999, Product engineering, *Chemical Engineering and Processing*, 38, 405-410.
10. S. Farrell, K. Jahan, R. Hesketh, J. Newell, M.J. Savelski, 2002, Introducing freshman engineering students to chemical product design, *Internacional Conference on Engineering Education*, August 18-21, Manchester, U.K.
11. P.M. Saraiva & R. Costa, 2004, A Chemical product design course with a quality focus, *Chemical Engineering Research and Design*, 82(A11), 1474-1484
12. A. W. Westerberg & E. Subrahmanian, 2000, Product design, *Computers & Chemical Engineering*, 24, 959-966.

13. R. Gani, 2004, Chemical product design: challenges and opportunities, *Computers & Chemical Engineering*, 28, 2441-2457
14. F. Štěpánek, 2004, Computer-Aided Product design. Granule dissolution, *Chemical Engineering Research and Design*, 82(A11): 1458-1466
15. I.E. Grossmann, 2004, Challenges in the new millennium: product discovery and design, enterprise and supply chain optimization, global life cycle assessment, *Computers & Chemical Engineering*, 29, 29-39
16. J.L. Cordiner, 2004, Challenges for the PSE community in formulations, *Computers & Chemical Engineering*, 29, 83-92
17. L. Constantine, K. Bagherpour, R. Gani, J.A. Klein & D.T. Wu, 1996, Computer Aided product design: Problem formulations, methodology and applications, *Computers & Chemical Engineering*, 20 (6/7), 685-702.
18. C. Wibowo & K.M. Ng, 2001, Product-Oriented process synthesis and development: Creams and pastes, *AIChE J.*, 47(12), 2746
19. R. Landau, 1997, Education: Moving from Chemistry to Chemical Engineering and beyond, *Chemical Engineering progress*, 93(1), 52-65.
20. L.A.Cisternas, M.A. Torres, M.J. Godoy & R.E. Swaney, 2003, Design of separation schemes for fractional crystallization of metathetical salts, *AIChE J.*, 49(7), 1731-1742
21. J.A. Caballero & I.E. Grossmann, 2001, Generalized disjunctive programming model for the optimal synthesis of thermally linked distillation columns, *Industrial & Engineering Chemistry Research* 40 (10): 2260-2274
22. M. Hustrup, R. Gani, Z. Kravanja, A. Sorsak & I. Grossmann, 2001, Integration of thermodynamic insights and MINLP optimization for the synthesis, design and analysis of process flowsheets, *Computers & Chemical Engineering*, 25 (1): 73-83 J
23. M.J. Zhu & M.M. El-Halwagi, 1995, Synthesis of flexible mass-exchange networks, *Chemical Engineering Communications*, 138: 193-211
24. V.M. Ashley & P. Linke, 2004, A novel approach for reactor network network synthesis using knowledge discovery and optimization techniques, *Chemical Engineering Research & Design*, 82 (A8): 952-960
25. N. Muro-Suñé, A. Munir, R. Gani, G. Bell, & I. Shirley, 2005, A framework for product analysis: Modelling and design of release and uptake of pesticides, in Puigjaner L, & A. Espuña, *European Symposium on Computer Aided Process Engineering-15*, Elsevier, Amsterdam. The Netherlands.
26. G. Agam, 1994, *Industrial Chemicals. Their characteristics and development*, Elsevier Science, Amsterdam, The Netherlands.
27. E. L. Cussler & G.D. Moggridge, 2001, *Chemical product design*, Cambridge University Press, Cambridge, United Kingdom.
28. V.G. Matta, P.B. Gomes, & A.E. Rodrigues, 2005, Optimization of perfume compositions, *Proceeding of the 4th. Mercosur Congress on Process Systems Engineering and 2nd. Mercosur Congress on Chemical Engineering*.

Chapter 16

Product Development – What to Make and How to Make

Ka Ming Ng^a, Rafiqul Gani^b, Kim Dam-Johansen^b

*^aDepartment of Chemical Engineering
the Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong, P.R. China*

*^bDepartment of Chemical Engineering
Technical University of Denmark
Building 229, DK-2800 Lyngby, Denmark*

16.1 INTRODUCTION

Chemical-based products cover a broad spectrum of materials and forms, ranging from molecules to appliances. Table 16.1-1 shows the various product functional forms, along with examples in major application areas. Examples highlighted in *italic* are those discussed in this book. Most small molecules such as BTX (benzene-toluene-xyxylene) are sold to chemical and allied products industries while a limited number such as refrigerants and solvents are for sale in the consumer market. In contrast, multicomponent liquid mixtures such as liquid shampoo, semi-solids such as cream and paste, and structured solids such as controlled release herbicide are often sold directly to the consumers. Business-to-consumer sale is even more prevalent for ready-to-use devices and appliances such as diagnostic kits, drinking water filters and air cleaners.

Small and functional molecules, and industrial products as typified by the examples in the bottom row of Table 16.1-1 have predominated traditional chemical engineering practice and education. Only recently have the design and manufacture of consumer-oriented chemical-products been getting the attention they deserve [1,2,3,4,5,6]. This shift from industrial to consumer products

Table 16.1-1. Classification of Chemical Products by Functional Form and Industrial Sector/End User with Examples.

Product Forms	Molecules		Structured / Multicomponent Products					
Industrial Sectors / End Users	Small Molecules	Functional Molecules	Gas and Aerosol	Liquid and Liquid Mixture	Cream and Paste	Simple and Structured Solids / Solid Mixture / Nanoparticle	Device / Package	Appliance, Equipment
Specialty Chemicals	Refrigerants, Fire suppressants, Lubricants	Dyes, Conditioners	Arsine	Solvent mixtures	NA	Metal sodium, Polymer composite	NA	NA
Agrochemicals	NA	Herbicides, Pesticides	Liquid herbicide	Liquid fertilizers	NA	Controlled release herbicides, Balanced fertilizers, Mosquito mat	Insect trap, Mosquito mat heater	Fertilizer granule spreader
Pharmaceuticals and Healthcare Products	NA	Active pharmaceutical ingredients	Inhalant	Syrups	Pharmaceutical creams	Injectable powders, Tablets, Dietary supplement formulations	Transdermal patch	Diagnostic kits
Foods, Flavors and Fragrances	NA	Sugar esters, Non-absorbing fat	Air freshener	Juice concentrate, Herbal extracts, Cooking oil	Ice cream, Tooth paste, Ketchup	Chocolate bar, Candies	Microwave ready food	Ice cream maker, Espresso machine
Personal Care Products, Cosmetics	NA	Surfactants	Hair spray	Shampoos, Hand antiseptics, Liquid detergent	Sunscreen lotions, Moisturizing cream	Powdered detergents, Bar soaps	Diapers, Adhesive dressing	Humidifier
Home and Office Products	NA	Colorant	Natural gas	Thinner	Polishing wax, Paint formulation	Toner, Paper, Glue stick, Low gas permeability film	Nanocomposite tennis balls, Gas sensors	Indoor catalytic air cleaners, Self-cleaning glass, Solar powered lamp
Industrial Products	Benzene, Toluene, Xylene	Polymer	Nitrogen, helium, oxygen	Heat transfer fluid	Petroleum wax	UF membranes, Catalyst, Silicon wafer	Gas meters	Fuel cells, Batteries

necessitates a sea change in perspective. It is no longer sufficient to focus on how-to-make, using process design and optimization to drive down the product cost.

More important for consumer products is what-to-make – the design of products with the functionalities and attributes to meet the needs and wants of the consumer. It may be that at the time of development, these wants are not clearly specified – that is, what the consumer wants without knowing it. This does not imply that processing is not important for consumer-oriented products which often possess complex internal structures and involve a wide variety of components. In fact, many opportunities exist for research on unconventional operations such as granulation, milling, emulsification, coating, etching, etc., which are the main unit operations in product-centered processing. Table 16.1-2 lists the various factors contrasting these two focuses – the traditional process-centered processing and the broadened product-centered processing.

Table 16.1-2. Comparison of Process-Centered and Product-Centered Processing

<i>Factors</i>	<i>Process-Centered</i>	<i>Product-Centered</i>
Nature of product	Simple molecules	Structured and complex products
Customers	Allied chemical industries	Consumers
Financial goal	Cost reduction / Improved profit of existing plants	New sources of revenue
Team	Primarily chemists and chemical engineers	A multidisciplinary team of marketing personnel, financial specialists, electronic and mechanical engineers, etc.
Product life	Decade	Month/Year
Product design	Minimum effort	Primary concern
Knowledge / Know-how	Well-structured	Fragmented (so far)
Technical focus	Engineering optimization	Engineering science
Unit operations	Traditional – distillation, crystallization, extraction, absorption, adsorption, etc.	Unconventional – granulation, milling, coating, etching, etc.
Thermodynamic database	Extensive	Limited

An alternative chemical product classification in terms of volume produced, cost, function of product and processing needs has been discussed in chapter 1.

One can observe that generally, bulk chemical products, produced in large amounts, need less regulatory control (that is, process conditions can be changed to match the product specification) and are generally very low cost. Specialty chemicals, produced in small amounts, need strict regulatory control (that is, process conditions cannot be changed once they have been registered) and are generally very expensive. Usually, the bulk chemicals serve as raw materials for the specialty chemicals and there is a large waste (that is, for a small amount of the chemical product, a large amount of bulk-chemicals are used). Chemicals based consumer products need bulk-chemicals as well as specialty chemicals.

The allure for the expansion of chemical engineering in this vast area of consumer-oriented products is clear. As traditional chemical engineering matures, the myriad technical challenges in product design and product-centered processing can stimulate fundamental research, and bring the discipline closer to practice, thereby creating job opportunities for our graduates.

There are a number of challenges in this effort. First, we need to identify a set of principles that each chemical engineer should know in order to function effectively in a typical consumer product sector. For example, a solid footing in interfacial phenomena and solids processing seems to be essential in product design. The integration of unconventional unit operations identified in Table 16.1-2 – granulation, milling, emulsification, coating, etching – with the traditional ones would be beneficial. Systematization and organization of such a body of knowledge might constitute the third paradigm of chemical engineering, if there is one. To identify the relevant unit operations, the truly essential principles and/or any yet-to-be-categorized features, the typical products and their manufacturing processes should be known in some detail. Thus, the second challenge is to collect all of this product and process information which, ideally, should come from experienced practitioners in the various industrial sectors. For example, in the textile and garment industry, the production of dyes, dyeing operations, fiber spinning, manufacture of wrinkle-free clothing, etc. are all part of the same value chain. Similarly, granulation, powder mixing, milling, tableting, etc. are required for the formulation of dietary supplements. For health foods, product safety is a major concern [7]. These industrial sectors normally receive scant attention in a typical chemical engineering curriculum. Third, since most consumer products have a relatively short life cycle, the market trend has to be followed before formulating a new product to meet the identified needs. In view of the multidisciplinary nature of and the time pressure on product development, effective project management is a critical factor in product management. Fourth, tools for predicting the physical and chemical properties of materials that are commonly used for chemical-based products are needed. For example, thermodynamic database for the

components in herbs and plants are currently incomplete or nonexistent. The case studies in chapters 2,6 and 9 also highlight these problems.

This book represents our effort to examine these challenges, particularly the second one, through case studies. They are by no means exhaustive. Not all products in Table 16.1-1 are discussed, and there are many product types and innumerable products that have not been covered in this book. Nonetheless, the following perspective for chemical-based product development can be envisioned.

Product development includes product design, and design of the corresponding manufacturing process. A product development project can be divided into three phases: Product conceptualization, detail design and prototyping, and product launch and manufacturing. The activities undertaken in each phase can be classified into five types –marketing, research and design, manufacturing, finance and economic analysis, and management. Figure 16.1-1 shows the classification of typical activities by phase and by type, which follows a similar scheme developed for products such as power tools, ink jet printers, cellular phones, and mountain bicycles, the manufacturing of which are normally handled by mechanical and industrial engineers [8].

These activities are discussed below with respect to the case studies presented in (chapters 2-14) in this book. The aim is to highlight what else needs to be done in the future.

16.2 PHASE 1: PRODUCT CONCEPTUALIZATION

Understanding customer needs (defined or still unrecognized), identifying product attributes, generating product concept, establishing product specifications, and synthesizing processing alternatives are the primary activities for phase 1 (Figure 16.1-1). Consider the air cleaner case study (chapter 12). Because of the widely publicized deterioration of air quality, a firm decides to manufacture a low-cost in-door catalytic air cleaner for home and office. A team with the necessary resources is formed. One of the key materials is a catalyst capable of decomposing VOCs to a very low concentration at room temperature. In research and design, the engineer proceeds to search for the best catalyst available on the market and in the patent literature, and to estimate the product cost. This scenario represents the conceptualization of a typical market-pull product. Often, the firm selects a product which branches out from an existing product line, leveraging its technical know-how and marketing experience. Such a product is referred to as a platform product. Not all product concepts originate from the marketplace.

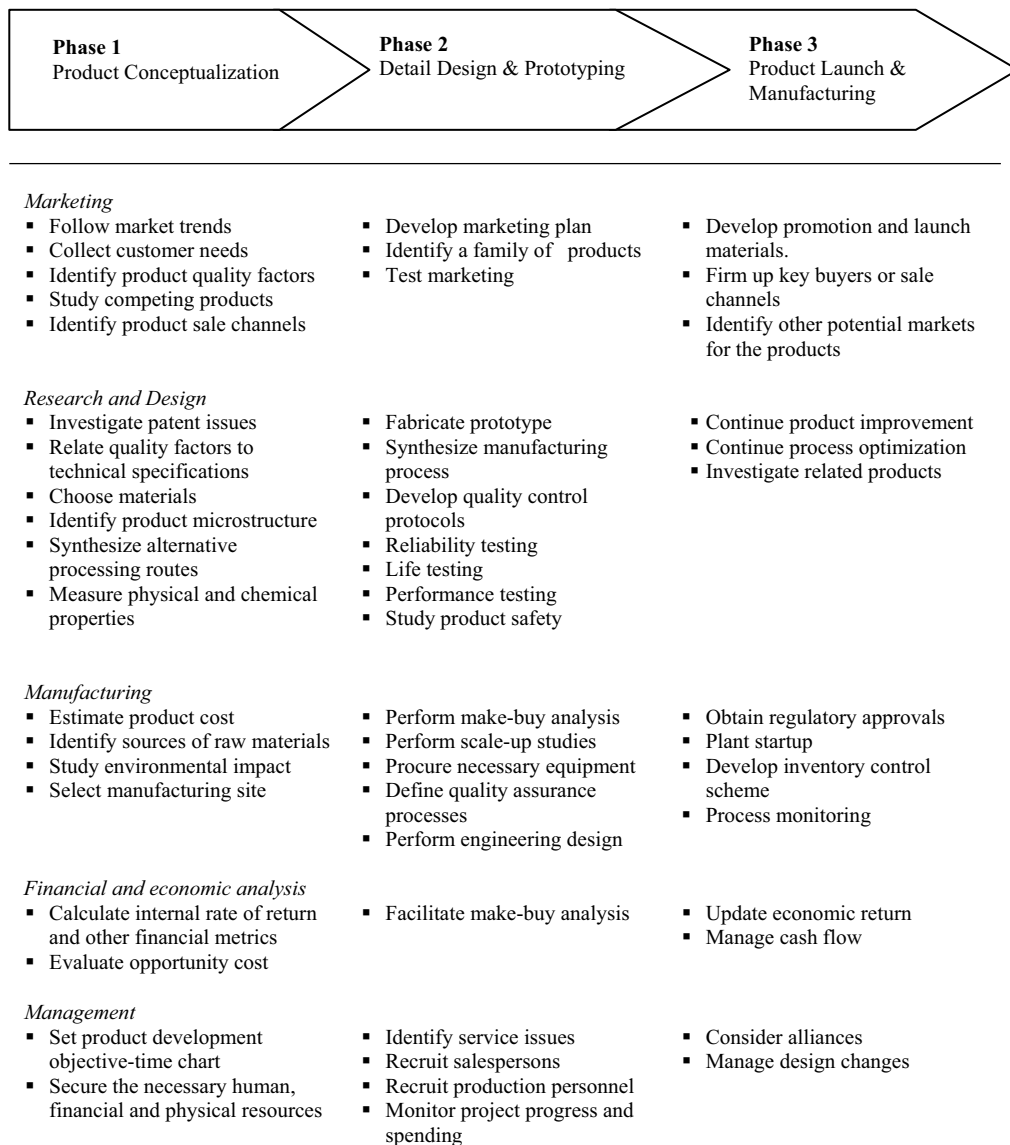


Figure 16.1-1. Classification of tasks for the development of chemical-based products by phase and by type.

New materials and/or processing techniques are being developed all the time in universities and research institutes. Most of these developments simply end up as a report in a trade magazine or technical journal. A subset may go for patent filing and eventually become a technology-push product. However, the probability of success is normally very low, the reason being that, without the guidance and support of a commercial firm, the project team can easily lose its sense of direction and commitment.

As shown in Table 16.1-1, products can be classified based on industrial sectors or end users. An obvious advantage of this classification is that similar processing techniques or scientific principles are involved in the design and manufacturing of these products. Thus, interfacial phenomena are highly relevant in the design of personal care products while GMP is of paramount importance in a pharmaceutical plant. Products can also be classified by functional form ranging from molecules to structured/multicomponent products. The latter are usually made up of a mixture of one or more active ingredients responsible for its functionality, and some supporting ingredients for enhancing its performance. Thus, pharmaceutical tablets often consist of active pharmaceutical ingredients and various excipients such as diluent, binder, disintegrant, lubricant, anti-adherent, glidant, pigment, and flavoring. Powder detergents consist of surfactants and various builders such as phosphates, anti-redeposition agent, fluorescent whitening agent, corrosion inhibitor, processing aid, fragrance, oxygen bleach, enzyme, fabric softener and suds control agent.

Regardless of the functional form, the product performance, characterized by a set of attributes referred to as the quality factors, is determined by two factors (Figure 16.2-1). The first one is the properties of the ingredients or mixtures (formulations), such as surface tension, viscosity, and so on. An active ingredient is typically selected according to the desired product functionality, while supporting ingredients are chosen to meet other quality factors. For example, a nonionic surfactant is preferred for baby shampoos because it is less likely than anionic or cationic surfactants to irritate the eyes. The fragrance should have subdued intensity for infants. The second factor is the product microstructure, which is characterized by structural attributes such as particle or droplet size distribution, phase volume fraction, dispersion/distribution of one ingredient in another ingredient, etc. For example, the ease of spread of low-fat margarine depends on how the water disperses in oil.

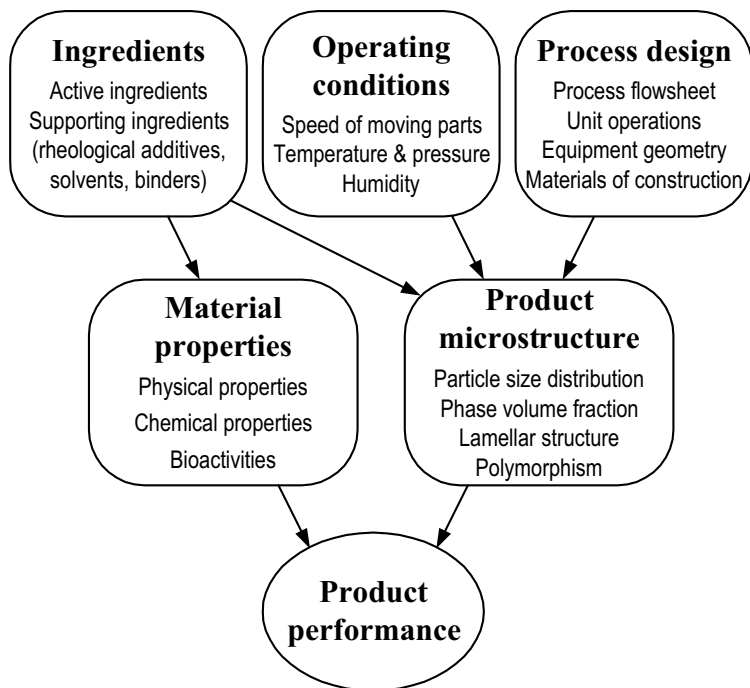


Figure 16.2-1. Factors determining product performance (after Wibowo and Ng, 2002).

For the devices, packages, appliances and equipments discussed in Table 16.1-1, clearly, microstructures have to be broadened to include relevant geometrical features. For example, geometry as well as micro-fabrication is the key in the design of MEMS (micro-electro-mechanical systems) devices. Disposable diaper is made up of several layers – a hydrophobic inner sheet to take in the fluid, an inner core of super-absorbent polymer and fluff pulp, and an outer nonporous film. All of these have to be properly designed to distribute the fluid evenly and rapidly throughout the diaper and to prevent possible leakage under pressure. Similarly, a typical commercial air cleaner (e.g., www.ncimfg.com) can perform multiple functions – dust removal by using filters and electro-filters, odor removal by oxidizing VOC using a honeycomb impregnated with catalysts, and bactericide using UV light. Of course, as the product expands from the chemical base, the project becomes a multidisciplinary effort with the participation of mechanical engineers, electrical engineers, and others. Although there are numerous examples of successful launches of chemicals based consumer products, it is still not certain if the optimal or best products have been found in any category. Much work is needed, specially model-based work

and employing past knowledge and expertise to improve future products through the application of systematic approaches to chemical product design.

Quality factors can be either qualitative or quantitative in assessing product performance. The sensorial qualitative factors such as convenience of use, smell and taste are qualitative. An arbitrary index is assigned to reflect the level of satisfaction which is often determined by an evaluation panel. As pointed out by Hill and Post (see chapter 9), several hundred people participated in the evaluation of the Dove® bar soap. This index is then related to the material properties and structural attributes via psychophysical models. Physicochemical, mechanical and rheological quality factors such as tensile strength, melting point, and viscosity are readily quantified. Table 16.2-1 shows examples of representative performance indices and standard methods of measurement for typical product quality factors. In the pharmaceutical, food and agrochemical industries, product quality management during the process operation is gaining increasing importance. Design and application of on-line monitoring techniques for product quality control (for example, Process Analytical Technology – PAT) therefore needs to be considered in the early stages of product-process design and development.

Another important activity for Phase 1 is estimation of product cost. To this end, the suitable processing technology and the associated manufacturing cost have to be determined. Many equipment items such as granulators, coaters, laminators, and homogenizers, and processes such as etching, sputtering, and milling have not been covered in sufficient detail in a traditional chemical engineering curriculum. A deeper understanding of the relationship between the design and operations of such equipment and the microstructure/geometry of the product represents a potentially fruitful area of research. Also, the equipment cost database for these processing units is rather incomplete as compared to the well-developed commercial software such as ICARUS (AspenTech) for traditional Chemical Engineering units. Again, this is another area in need of further development.

From the management point of view, it is important to outline all the steps and devise various contingency plans for the entire product development project. For this purpose, the RAT²IO module and the objective-time chart can be of use [9]. RAT²IO stands for resources, activity, time, tools, input/output information, and objective (Table 16.2-2).

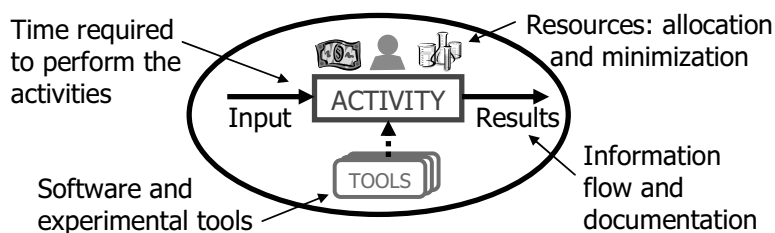
Table 16.2-1. Performance indices for typical chemical-based product quality factors [5].

Quality factor	Product form							Performance index
	Compo- site	Tablet/ capsule	Powder/ Granule	Cream/ Paste	Viscous liquid	Dilute liquid	Aerosol	
Sensorial quality factors								
Visual appearance: transparent, opaque, pearlescent, color	✓	✓	✓	✓	✓	✓	✓	Arbitrary indices based on panelist evaluation
Smell: fragrant, odorless, stinky	✓	✓	✓	✓	✓	✓	✓	
Taste: sweet, sour, bitter	✓	✓	✓	✓	✓	✓		
Sense upon application: smooth, oily, sticky				✓	✓	✓		
Physicochemical quality factors								
Product stability (resistance against creaming)				✓	✓	✓	✓	Shelf life
Ability to change phase upon application	✓	✓	✓	✓	✓			Melting point, glass transition temperature
Hygroscopicity	✓	✓	✓	✓	✓	✓		Moisture absorption rate
Ease of dispersion in a liquid			✓					Wetting time
Ability to dissolve in a liquid	✓	✓	✓					Dissolution time
Rate at which an active ingredient is released	✓	✓	✓	✓	✓	✓		Release time
Mechanical quality factors								
Resistance to failure	✓	✓	✓					Tensile strength
Resistance to indentation (hardness)	✓	✓	✓					Hardness numbers
Ease of failure by fracture (toughness)	✓	✓	✓					Fracture energy
Elasticity	✓	✓	✓					Young's modulus
Rheological quality factors								
Ease of spreading when rubbed onto a surface, applied by brush, or shaken				✓	✓			Viscosity at application shear rate
Ability to flow under gravity				✓	✓			Yield value

Table 16.2-2. Elements of the RAT²IO Module

Define O bjective of the task
Specify the input and output I nformation
Identify the A ctivities to be performed
Identify appropriate T ools
Identify human and monetary R esources to perform the activities
Estimate the T ime needed to meet the objective

Each task in Table 16.2-1 is executed with a clear objective in mind. One has to identify the available input information and the desirable outcomes along with the necessary activities to achieve these outcomes. Execution of such activities requires a competent team with the requisite skills. As all managers know very well, the recruitment, motivation and retention of the best team can be a constant struggle. The availability of financial resources is a necessary but not a sufficient condition. Consider the accessibility of various equipment and software needed for a product development project. In principle, all equipment can be purchased; in practice, equipment acquisition and installation, and operator training can take an excessively long time. It is far better to use existing infrastructures and technology providers, either internal or external of the company, if they are available. It is exceedingly difficult to accurately estimate the time for each task as many stories on project delay and cost overrun can testify. Outsourcing is expected to help complete the development project in a timely fashion. The elements of the RAT²IO module are depicted in Figure 16.2-2.

Figure 16.2-2. Depiction of the RAT²IO Module

To minimize the total project time, from product conceptualization to product launch, one has to go beyond an accurate estimation of the time required to

finish each task. Tasks that can be performed concurrently should also be identified. Consider the objective-time chart in Figure 16.2-3, which shows a product development project with four main tasks. Task A is started first while Tasks B and C can be performed in parallel. Each main task such as D can be further decomposed into subtasks such as D1 to D6. Each subtask such as D4 can be further refined into its own subtasks. The objective-time chart is different from the traditional Gantt chart in that, it shows the subtasks in a hierarchical manner and is much richer in content with the RAT²IO module.

Whether a task can be performed concurrently with other tasks depends on two factors. One is whether the input information for the activity under consideration depends on the output from other activities. The other is the availability of manpower and equipment. Consider a team that has only one chemical engineer to design both the reactor and the crystallizer. Even though reaction kinetics, solid-liquid equilibrium data and crystallization kinetics can be measured in parallel, the total time for these activities is determined by what the single individual can achieve.

Observation of actual practice indicates that the RAT²IO module and objective-time chart are seldom used fully and explicitly, particularly for new products and processes. Instead, the experienced project manager often guides the team or a subset of the team to execute the necessary activities in a step-by-step manner. The advantage is twofold. First, a lot of information is not known at the start of the product development project. It is better to just define the main tasks and avoid making too many assumptions in order to specify the subtasks. Second, the team members assigned for a subtask are normally specialists for that certain activity. It is far easier to leave the management of the corresponding RAT²IO module to this sub-group from an organizational point of view.

16.3 PHASE 2: DETAILED DESIGN AND PROTOTYPING

Fabrication of the prototype is an important step in product development. It demonstrates that the various components can indeed be physically integrated to form the final product with the desired functionalities. Consider a UV sensor. While its functionality depends on the physical response of a certain nanomaterial in the presence of UV light, an electric circuit and a display system are required for a functional consumer product. The availability of a prototype is essential in test marketing, safety tests, reliability tests and so on. However, the development of consumer-oriented products often involves a considerable amount of trial-and-error, which can lead to costly delays in product launching [10].

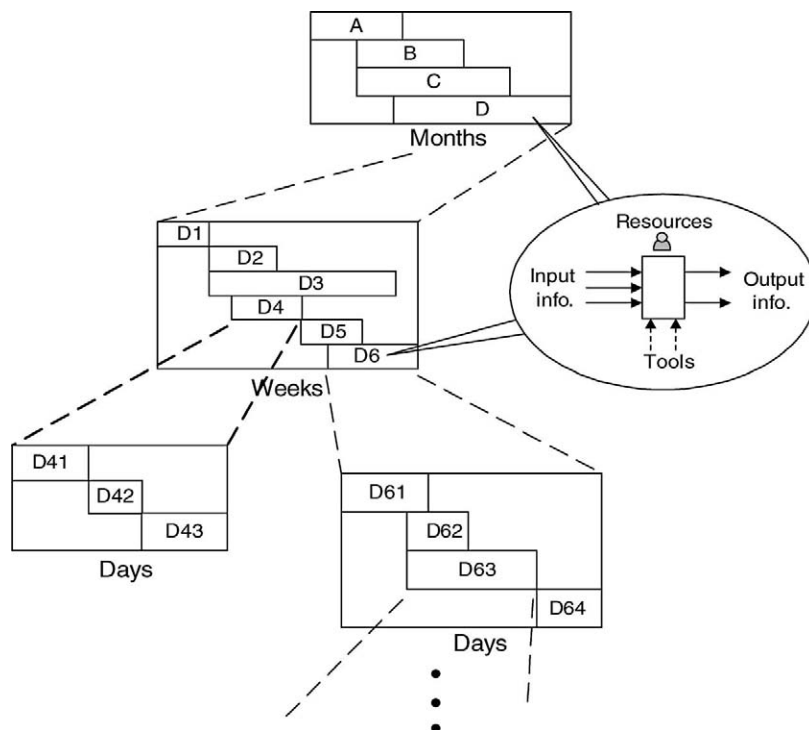


Figure 16.2-3. An objective-time chart which breaks down a task into subtasks each of which can be represented by a RAT²IO module.

Another key task is detailed design. One can build on the prototype design to lay down the complete specifications of the final product. Product packaging which can greatly enhance consumer appeal should also be considered at this point. Sourcing of all the necessary materials and components should be thoroughly investigated. Make-buy decisions can significantly impact the final product cost, as well as the necessary investment. Obviously, these decisions depend on the company goal, its financial situation, and product life. The corresponding manufacturing process is likely to be batch and discrete in nature. A potential problem is the difficulty in scaling up a laboratory procedure to large scale commercial production.

To put things in perspective, let us consider the cost breakdown of a typical hair care product. The surfactant, polymer and other raw materials constitute around 10% of the producer price. Other costs include processing at around 5-10%, packaging at around 10-15%, administration and R&D at around 5-10%, and

marketing at around 50-55% of the producer price. Clearly, a properly executed marketing plan is crucial to the success of a consumer product.

16.4 PHASE 3: PRODUCT LAUNCH AND MANUFACTURING

Thus, it is highly desirable that key buyers and sales channels have already been locked up by the time of product launch. Inevitably, customers, process engineers, financial officers, and other stakeholders request various design changes. Proper change control is essential to avoid unacceptable delays and cost overruns.

While the length of product life varies from product to product, the selling price generally falls as imitation products begin to appear on the market. To maintain the profit margin, the raw material cost and/or the manufacturing cost have to come down. Alternatively, improved products can be designed to hold the price and maintain market share. Both of these R&D activities have to be continued throughout the life of this product platform.

16.5 FUTURE CHALLENGES

Chemical-based products have been gaining significance in the global chemical industry. Various aspects of these diverse industrial sectors have been discussed in this book. The expansion from molecules and industrial products, to structured solids and consumer products, as represented by the lower left and upper right triangles of Table 16.1-1, respectively, is a natural progression. The chemical engineering principles – thermodynamics, heat, mass and momentum balances, etc. – as well as the supporting subjects – chemistry, biochemistry, biology, and economic analysis, etc. – remain the same. The differences, and thus the opportunities for further development, can be gleaned from the case studies and the three phases of product development presented in Figure 16.1-1. These are summarized below. Current research on chemical engineering sciences, optimization, and process design that can be extended to product development will not be discussed here.

I. Product Attributes in Different Industrial / Product Sectors

As demonstrated by the case studies on food [see chapter 6], and cosmetics and toiletries [see chapter 9] products, the desired product attributes are very different from those of commodity chemicals. The key requirement for simple molecules is purity. For functional molecules such as those used as in hair conditioner, the functional groups of the molecule, be it cationic, anionic or nonionic, and the flexibility of the molecular backbone have to be tailored to meet the needs. By and large, the number of requirements increases with the

structural complexity and the number of essential components in the product. Also, a consumer product tends to involve more qualitative quality factors. Identification and systematization of these product attributes, classified by industrial sector if appropriate, is an important step in product design.

II. Structural Attribute-Material Property-Product Attribute Relationships

The second challenge is to relate the desired product attributes to the material properties of the ingredients and the structure of the product. For example, the development process would have been much more efficient if a model was available to describe the behavior of cleansing bars and structured food products. Without the benefits of predictive models, as is the present status for many consumer products, extensive trial-and-error by experiments are required. Even if a comprehensive model based on first principles is not available, a combination of physical insights and heuristics can still help improve the development process. Chapters 1-2 report some new developments in this area. See also [11] for a more detailed discussion on the issues and needs related to the roles and uses of property models in product design.

III. Structural Attribute-Processing Relationships

A related challenge is to link the desired structural attributes to the equipment and its operating conditions. Consider the manufacture of granules for a controlled release formulation in a granulator. Because of the complex equipment design, interacting physicochemical phenomena, and the variety of materials involved in granulation, it is not possible to predict the operating conditions under which granules of the desirable particle size distribution, porosity, etc. can be produced. This is despite the fact that much of the underlying physics has been elucidated in the past decade. Similar issues can be found in the manufacture of low-fat margarines, nano-particles, aligned carbon nano-tube devices, etc. On-line process monitoring will find increasing applications in high-value product quality management and they will need to be addressed in the early stages of product-process development.

IV. Assessment and Elucidation of Qualitative Quality Factors

Customer delight is a key requirement for consumer products. For example, the hand-feel of a fabric is an important measure of its quality. There exist many challenges to determine these quality factors in a more scientific way. However, even if only a semi-quantitative measurement can be devised, this can yield insights on how the underlying material or structural attributes control the quality factor. These insights can in turn be used to formulate innovative products.

V. Thermodynamic Database and Predictions

The existing thermodynamic database focuses on the commodity chemicals sector. Only limited information is available for the ingredients in

pharmaceuticals and herbs. The problem for natural products is compounded by the fact these herbs contain a large number of components, leading to difficulties in separation and purification. A more comprehensive database, along with predictive software, can be highly beneficial to product and process design. Also, generated data from molecular modeling should be stored in databases and made available to others so that duplication of these time consuming computations can be avoided.

VI. Multiscale Analysis

It should be clear from all the case studies that product development involves technical issues ranging from the molecular scale to the plant scale. To handle the product development project effectively, it is necessary to consider issues in different aspects and scales, and integrate them in a systematic [12]. Again, let us consider granulation. To properly design the product and the process, one has to account for the properties of constituent powder, the binder, the operations of the granulator, and the solids processing plant around the granulator [13].

VII. Interface between Engineering, and Business and Management

Traditionally, chemical engineers primarily participate in cost estimation. As the three phases of product development indicate, the consumer product sector demands closer ties to marketing and management, which play a key role in making the project a success. How far a chemist or chemical engineer should venture into these activities is unclear. However, armed with knowledge on the effects of materials and processing on product attributes, the chemist/engineer is in a good position to contribute to product conceptualization and marketing. The engineer's understanding of the various activities in the form of the RAT²IO module is of paramount importance in project planning. It is well-known that an engineer can be trained to be a business manager but not the other way around. The choice is in our hands.

ACKNOWLEDGMENT

The financial support of RGC Grant (HKUST 602703) for this work is gratefully acknowledged by KM Ng.

REFERENCES

1. Tanguy, D., and P. Marchal, "Relations between the Properties of Particles and Their Process of Manufacture," *Chem. Eng. Res. Des.*, **74**, 715 (1996).
2. Villadsen, J., "Putting Structure into Chemical Engineering," *Chem. Eng. Sci.*, **52**, 2857 (1997).
3. Winternantel, K., "Process and Product Engineering: Achievements, Present and Future Challenges," *Chem. Eng. Res. Des.*, **77**, 175 (1999).
4. Cussler, E. L., and J. D. Moggridge, *Chemical Product Design*, Cambridge University Press (2001).
5. Wibowo, C., and K. M. Ng, "Product-Centered Processing: Chemical-Based Consumer Product Manufacture," *AIChE J.*, **48**, 1212 (2002).
6. Seider, W. D., J. D. Seader, and D. R. Lewin, "Product and Process Design Principles – Synthesis, Analysis, and Evaluation," 2nd Edition, Wiley, 2004.
7. Bombardelli, E., and V. Bombardelli, "Twenty Years' Experience in the Botanical Health Food Market," *Fitoterapia*, **76**, 495 (2005).
8. Ulrich, K. T., and S. D. Eppinger, "Product Design and Development," second edition, Irwin McGraw-Hill, Boston (2000).
9. Ng, K. M., "MOPSD: a framework linking business decision-making to product and process design," *Comp. Chem. Eng.*, **29**, 51 (2004).
10. Pisano, G. P., *The Development Factory*, Harvard Business School Press, Boston, MA (1997).
11. Gani, R., Chemical product design: challenges and opportunities, *Computers & Chemical Engineering*, **28**, 2441-2457 (2004).
12. Li, Jinghai, and Mooson Kwauk, "Exploring Complex Systems in Chemical Engineering - the Multi-scale Methodology," *Chem. Eng. Sci.*, **59**, 521 (2003).
13. Wibowo, C., and K. M. Ng, "Synthesis of Bulk Solids Processing Systems," *AIChE J.*, **45**, 1629 (1999).

Subject Index

Accelerated exposure testing (chapter 7)	206
Active ingredient design/selection	452
Activity measurements (chapter 11)	331
Activity test (chapter 11)	325
Adhesion test	203
Adsorbent formulations	377
AF Paint registration/regulation schemes	230
Air dehumidification system	384
Air filtration system	384
Air flow and noise measurements	397
Air handling system	383
Air purification system	384
Amorphous silicon films	295
Amorphous solid state	35
Analytical techniques for crystallization design	48
Approval of paint products	230
Assessment and elucidation of qualitative quality factors	487
Backbone generation (case study 2 – chapter 14)	443
Background (chapter 12)	344
Batch manufacturing	26
Binder selection	285
Binder system	197
Bioaerosol removal and remediation	402
Biocide release measurements	212
Biocides	197
Blister box test	206
Brainstorming (chapter 12)	357
Business plan (chapter 12)	357
CAMD techniques	435
Candidate selection (chapter 5)	155
Case studies (chapter 1)	15
Case studies in chemical product design	417

Case studies in chemical product design (CAMD)	435
Case study - replacement of ethyl glycol	94
Case study – replacement of ethyl glycol acetate	92
Case study – Solubility modeling and crystallization process design for cimetidine	56
Case study 1: Cooling crystallization solvent design	131
Case study 2: Drowning-out crystallization solvent design	138
Cash flows and profitability analysis (chapter 10)	308
Catalyst activity	316
Catalyst and Adsorbent	375
Catalyst design – evaluation of results	338
Catalyst design results	331
Catalyst formulation (chapter 12)	375
Catalyst optimization (chapter 12)	376
Catalyst preparation and characterization (chapter 12)	375
Catalyst-Adsorbent monolith wheel (chapter 12)	379
Characterization of antifouling paint	190
Characterization of marine biofouling	182
Charity home for handicapped children (chapter 12)	411
Chemical engineering education in Hong Kong	347
Chemical engineering in Hong Kong and Southern China	346
Chemical products classifications	464
Chemical product – process design	2
Chemical product design educational modules	17
Choice of co-surfactant	285
Cimetidine crystallization process design with NRTL-SAC	72
Cimetidine results for NRTL-SAC	61
Cimetidine solubility study with SoluCalc	69
Clarifying objectives (chapter 12)	380
Company formation (chapter 12)	365
Competitor analysis (chapter 12)	363
Computer aided molecular design	87
Consequences of biofouling	184
Constantinou-Gani group contribution method	89
Critical path analysis (chapter 12)	355
Crystal morphology (chapter 4)	119
Crystal structure and polymorphism	33
Crystal structure prediction	37

Crystallization process design	47
Crystallization science	28
Crystallization solvent design	117
Customer requirements (chapter 12)	382
Cyclic blister box test	206
Decision mapping, decision table & effort impact graph	356
Decomposition based solution methodology (chapter 4)	123
Definition of product goals	12
Dehumidification test	398
Design a liquid detergent enzyme product	153
Design and development of chemical products	7
Design methodology (chapter 5)	153
Design of a molecule or mixture in chemical product design	6
Design of a new sulfuric acid catalyst	315
Design of active pharmaceutical ingredients	23
Design of chemical products	465
Design of controlled release antifouling paints	181
Design of Dove® beauty bar	275
Design of industrial catalysts	311
Design of liquid enzyme products	149
Design of manufacturing process (chapter 8)	258
Design strategy (chapter 11)	322
Designing API crystallization processes	44
Dessicant	378
Detergents (chapter 8)	239
Determining characteristics	383
Development of rate expression (chapter 11)	330
Differential scanning calorimetry (DSC)	50
Differential vapor sorption (DVS)	50
Disappearing polymorphs - Ritonavir	42
Discussion of results (Dove® beauty bar)	284
Docking of 4-formylphenyl boronic acid into the binding pocket of a subtilisin	156
Drag resistance	209
Drug design	453
Dynamic simulation of paint behavior	218
Dynamic testing using rotary set-up	207
Economics – profitability analysis	307

Enantiotropy and monotropy	36
Entrepreneurship and product design	343
Enzyme kinetics and determination of K_i in a buffer system	157
Epitaxial silicon films	302
Epitaxial silicon wafers	289
Establishing functions (chapter 12)	380
Evaluating alternatives (chapter 12)	389
Evaluation in chemical product design	10
Example 1 – automatic dishwashing (ADW) tablet with gelatinous inner-portion	263
Example 2 – Sachet household cleaning detergent	266
Example 3 – Non-aqueous structured liquid laundry detergent	269
Experimental model inputs (chapter 7)	226
Fixed operating costs (chapter 10)	308
Flammability limit of the solvent (chapter 4)	120
Food process flow diagram	173
Formulation (chapter 1)	27
Formulation and paint production	197
Framework for product-process design	14
Full paint system on a ship	193
Full ship testing	212
Full-scale test production (chapter 11)	329
Future challenges (product development)	486
Generating alternatives (chapter 12)	385
Generic competitor strategy (chapter 12)	364
Geological, historical and cultural background of Hong Kong	344
Global anti-fouling paint legislation	232
Group contribution methods	87
High pressure liquid chromatography (HPLC)	51
High Tech Entrepreneurial Program (HTEP) – chapter 12	348
Historical aspects of antifouling	185
HKUST University Canteen (chapter 12)	406
HTEP Team Organization (chapter 12)	351
Hydraulic mandrel bening test (MAN-H)	205
Ibuprofen	137
Ideal solubility (chapter 2)	52
Ideas (Case studies in chemical product design)	422
Identification of process alternatives	13

Identification of product candidates	12
Identification of product quality factors	240
Immersion	207
Impact	204
Importance of crystallization	26
Important issues and needs in chemical product design	12
Impregnation and calcination	324
Improving details (chapter 12)	390
Impurities and nucleation	31
Indoor air quality	367
Indoor air survey	370
Industrial catalysts	311
Industrial stability test	337
Input-output structure (chapter 6)	171
Interface between engineering, and business and management	488
Integration of product-process design	3
Investment (chapter 10)	307
Kinetics of crystallization	30
Laboratory and field tests – Field performance data	405
Laboratory and field tests – Laboratory performance data	394
Laboratory evaluation	48
Liquid detergent stablization system	149
Liquid state of the solvent (chapter 4)	121
Mandrel bending test	205
Manufacturing process	302
Manufacturing requirements (chapter 12)	383
Marine biofouling	182
Marine biofouling protection	181
Market analysis (chapter 12)	359
Market needs (chapter 12)	359
Market survey (chapter 12)	360
Marketing requirements (chapter 12)	383
Mathematical models (chapter 7)	217
Mechanical testing	203
Mechanical strength (chapter 11)	320
Mechanical strength (chapter 11)	334
Microscopical examination of paint (MEP)	215
MINLP model (chapter 4)	122

Mixture design (additive for paints)	454
Mixture design (chapter 14)	455
Mixture design (chapter 4)	124
Molecular or mixture design	15
Multiscale analysis (chapter 12)	488
Nature of chemical products	459
Needs (Case studies in chemical product design)	418
Nuclear magnetic resonance (NMR) spectroscopy	51
OPT-CAMD	126
Optical and scanning electron microscopical examination of paint	215
Optimal design of PECVD reactor	293
Optimization technique (chapter 3)	90
Other chemical products	8
Other legislation covering paint products	232
Other specifications (chapter 12)	385
Paint components	190
Paint production	199
Paint testing	202
Painting ship hulls	201
Performance requirements (chapter 12)	382
Pharmaceutical industry – introduction	24
Pharmaceutical products	115
Phase 1 Products Conceptualization (chapter 16)	477
Phase 2 Detail Design and Prototyping (chapter 16)	484
Phase 3 Product Launch and Manufacturing (chapter 16)	486
Pigment volume concentration (PVC)	198
Plasma-enhanced chemical vapor-deposition	289
Polymer design (case study 3 – chapter 14)	447
Polymorph screening	44
Polymorph stability	45
Polymorphism	33
Polymorphism and API product design	37
Polymorphism, nucleation and growth	38
Potential recovery (chapter 4)	118
Practical methods for controlling polymorphic form	38
Prediction of pure component properties	87
Pressure drop (chapter 11)	321
Pressure drop (chapter 11)	336

Primary nucleation	30
Problem definition (chapter 5)	153
Problem solution (Dove® beauty bar)	281
Problem solution strategy (Dove® beauty bar)	279
ProCAMD (chapter 4)	130
Procedure for product development (detergents)	240
Process Analytical Technology	482
Process design versus product design (chapter 6)	169
Process synthesis	167
Process synthesis methodology (chapter 6)	170
Processing (Dove® beauty bar)	284
Product attributes in different industrial/product sectors	486
Product description and production strategy	357
Product design 1 (chapter 12)	386
Product design 2 (chapter 12)	386
Product design 3 (chapter 12)	387
Product design criteria of an antifouling paint	192
Product design methodology	88
Product design problem (Dove® beauty bar)	276
Product development	473
Product formulation (chapter 8)	244
Product identification and evaluation	16
Product manufacture (chapter 13)	431
Product quality (chapter 1)	25
Product-centered process synthesis and development	239
Production (chapter 11)	322
Production carrier (chapter 11)	324
Production of sulfuric acid	312
Product-process evaluation	13
Project 1: Optical currency substrate for counterfeit prevention	418, 422, 428, 431
Project 2: Food wrap	418
Project 3: Controlled drug release	420
Project 4: Solid formulation of low melting point active ingredient	420, 423
Project 5: UV shield film	420
Project 6: Adhesives for wet metal surfaces	421,

	426, 429
Project description (chapter 12)	350
Prototype design – Assembly and test of prototype units	391
Prototype design - Rational design approach	380
Prototype unit design 1	392
Prototype unit design 3	393
Public clinic for the elderly	409
RAT2IO module	483
Refrigerant design (case study 4 – chapter 14)	450
Regional and local schemes	231
Regulation and manufacturing flexibility	26
Research challenges – food products and processing	178
Role of crystallization & solubility modeling	23
Safety requirements	382
Scanning electron microscopy coupled with energy-dispersive X-ray analysis (SEM-EDX)	215
Schematic overview of alternative food process	178
Seawater-soluble pigments and their potential use in antifouling paints	222
Secondary nucleation	33
Seeding (chapter 2)	32
Selection (Case studies in chemical product design)	428
Selection of additives (chapter 8)	249
Selection of partially hydrogenated Sodium Cocoyl Isethionate (SCI)	284
Selection of product form (chapter 8)	246
Selection of surfactant system (chapter 8)	248
Setting requirements (chapter 12)	381
Simulation of the effect of paint formulation parameters on the antifouling paint behavior	217
Simulation tools (chapter 7)	217
Single compound design (chapter 4)	123
Site air quality survey	372
Site modeling	370
Site selection criteria	370
Skill matrix and team working	356
Solid-liquid equilibria	29
Solubility (chapter 4)	118
Solubility measurement and solvent screening	45

Solubility modeling	52
Solution approaches (product-process design)	5
Solvates and hydrates	34
Solvent design for crystallization	115
Solvent design-selection (case study 1 - chapter 14)	436
Solvent effects on nucleation and growth	32
Solvent identification with ProCAMD (case study 1 – chapter 14)	437
Solvent selection (chapter 2)	46
Solvents (chapter 7)	197
Some observations of the nature of chemical products	461
Stage-Gate product development process (chapter 10)	290
Stages of chemical product-process design	4
Static performance testing	211
Step 1- Concept development (chapter 10)	290
Steps 2-5 – Feasibility, development, manufacturing, and product introduction (chapter 10)	292
Storage stability trials in model liquid detergent	158
Structural attribute-material property-product attribute relationships	487
Structural attribute-processing relationships	487
Structure of ice cream	168
Structured food products	167
Structured product formulation and design	16
Structured products and formulations	7
Supersaturation (chapter 2)	29
SWOT and VIRO analysis	362
Task identification (chapter 6)	171
Team management tools 101 (chapter 12)	355
Team organization and resource (chapter 12)	351
Test of deactivation (chapter 11)	329
Test of mechanical strength (chapter 11)	327
Test of pressure drop (chapter 11)	328
Testing of candidates (chapter 5)	155
The local UNIFAC approach	55
The NRTL segment activity coefficient method	53
Thermodynamic database and predictions	488
Thermodynamics and crystallization	28

Thermogravimetric analysis (TGA)	50
Thixotropic agents	198
Time management	355
Tin-free systems	225
Toxicity of the solvent (chapter 4)	120
Unit operation (chapter 6)	172
Using the NRTL-SAC model in Aspen Properties	59
Variable operating costs (chapter 10)	308
Viscosity of the solvent (chapter 4)	121
VOC removal and remediation	398
VOCs adsorbent	377
Wetting agents	198
What to make and how to make	473
Wooden block settings	205
Working mechanisms of antifouling paints	194
X-ray diffraction (XRD)	48

Author Index

Author	Chapter	Page
Luke E.K.Achenie	4	115
Keith K.H. Choy	13	417
Kurt A. Christensen	11	311
Luis A. Cisternas	15	459
Leonidas Constantino	3	87
Peter Crafts	2	23
Kim Dam-Johansen	1, 7, 16	1, 181, 473
Rafiqul Gani	1, 14, 16	1, 435, 473
Michael I. Hill	9	275
Arunprakash T. Karunanithi	4	115
Søren Kiil	7	181
F. Michiel Meeuse	6	167
Ka Ming Ng	1, 8, 16	1, 239, 473
Lone Kierstein Nielsen	5	149
Albert J. Post	9	275
Warren D. Seider	10	289
Ole Simonsen	5	149
Talid Sinno	10	289
Vassilis Vassiliades	3	87
Claus E. Weinell	7	181
Diego M. Yebra	7	181
King Lun Yeung	12	343